SECTION 1

Functional Anatomy of the Serotonergic System
CHAPTER 1.1

Evolution of Serotonin: Sunlight to Suicide

Efrain C. Azmitia *

Department of Biology and Psychiatry, Center for Neuroscience, New York University, Washington Square East, New York

Abstract: Serotonin is involved in many of the behaviors and biological systems that are central to human life, extending from early developmental events related to neurogenesis and maturation, to apoptosis and neurodegeneration that underlie dementia and death. How can a single chemical be so powerful in determining the quality and quantity of human life? In this chapter, the evolution of serotonin and its biosynthetic pathways from tryptophan are examined. The essential components of the serotonin biosynthetic pathway are highly conserved. Tryptophan-based chemicals, including serotonin, melatonin and auxin, have important action in the differentiation, mitosis and survival of single cell organisms. As the complexity of life evolved into multicellular organisms, especially plants, serotonin levels rose dramatically. The importance of tryptophan, serotonin and auxin is evident in photosynthesis and plant growth. When the animal kingdom began, the ability to synthesize tryptophan was lost, and serotonin levels dropped accordingly. Animals had to develop many special mechanisms to secure tryptophan from their diets, and to carefully conserve its integrity during circulation throughout the body. There was the emergence of multiple receptors and reuptake proteins that permit serotonin actions without utilization of serotonin itself. Serotonin receptors appear as early as the blastula and gastrula stages of embryonic development, and continually monitor and regulate ontogenic changes as it serves phylogenetic evolution.

The most amazing concept to emerge from an analysis of serotonin evolution is its relation to light. Beginning with the light-absorption properties of the indole ring of tryptophan, a direct path can be drawn to the effects of sunlight on photosynthesis and serotonin levels in plants. Progressing further in phylogeny, the effects of sunlight are seen on serotonin levels and on mood, sleep and suicide ideation in humans. The focus on the evolution of serotonin leads from an awareness of the beginning of life to the current human struggle to enjoy our dominant position on earth.

Keywords: seasonal affective disorder (SAD), tryptophan, auxin, hallucinogens, 5-HT1A receptor, photosynthesis, homeostasis indole, chloroplast, fungus, metazoa.

Introduction

It has always been an enigma how serotonin, a monoamine neurotransmitter, can have such diverse and important functions in the human brain. The question is further complicated when it is recognized that serotonin exists in all the organs of the body (e.g., the skin, gut, lung, kidney, liver, and testis) and in nearly every living organism on Earth (e.g., fungi, plants, and animals) (Azmitia, 1999). Serotonin is phylogenetically ancient, and evolved prior to the appearance of neurons. Whatever function serotonin has in the brain, it should be consistent with its evolutionary history. However, little attention has been given to the biological emergence of serotonin. Most neuroscience studies focus on serotonin in mediating particular behaviors (e.g., feeding, sex, sleep, and learning) or its involvement in specific brain disorders (e.g., depression, Alzheimer’s disease and autism). A broader view has been rarely raised. Over the past 50 years, several scientists have proposed general organistic roles for brain serotonin (Brodie and Shore, 1957; Woolley, 1961; Scheibel et al., 1975). A more comprehensive theory that includes expanded functions proposes that serotonin acts as a homeostatic regulator which integrates mind and body with the outside world (Azmitia, 2001, 2007). In reading this chapter, it is hoped that the reader will appreciate why serotonin came to be so important in the mental health of humans.

The evolution proposed for serotonin begins with a discussion of its precursor tryptophan and its metabolites in unicellular organisms nearly 3 billion years ago. To make serotonin from tryptophan, oxygen is needed, and in the earliest geological times the Earth’s atmosphere had little oxygen. Thus, serotonin is made specifically
4  Functional Anatomy of the Serotonergic System

Table 1  Light spectrum of wavelengths that reach the Earth

<table>
<thead>
<tr>
<th>Type</th>
<th>Wavelength (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrared</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Red</td>
<td>700–630</td>
</tr>
<tr>
<td>Orange</td>
<td>630–590</td>
</tr>
<tr>
<td>Yellow</td>
<td>590–560</td>
</tr>
<tr>
<td>Green</td>
<td>560–490</td>
</tr>
<tr>
<td>Blue</td>
<td>490–450</td>
</tr>
<tr>
<td>Violet</td>
<td>450–400</td>
</tr>
<tr>
<td>UVA</td>
<td>380–400</td>
</tr>
<tr>
<td>UVB</td>
<td>315–380</td>
</tr>
<tr>
<td>UVC</td>
<td>280–315</td>
</tr>
</tbody>
</table>

in unicellular systems capable of photosynthesis and the cellular production of oxygen. The conserved serotonin biosynthetic pathway began in the unicellular systems of cyanobacteria, green algae and fungi, and continually evolved to its current position in the human brain.

Photosynthesis is dependent on the energy derived from sunlight. The amount of light reaching Earth has seasonal variation and, because of the Earth’s tilting, is most noticeable at the polar extremes. Light can be roughly divided into ultraviolet (UV) and visible light (Table 1). In humans, UVB radiation produces sunburn and some forms of skin cancer, while UVA (black light) will produce skin discoloration and is necessary for vitamin D production. Glass and plastic can block UVB rays. The two types of light mainly absorbed during photosynthesis in plants are blue light and red light. The light most effective in alleviating the depression associated with seasonal affective disorder is blue light.

Tryptophan

Light capturing

Indole

Indole is an organic compound consisting of a benzene ring and a pyrrole ring (Figure 1). The origin of the first photosynthetic pathway is proposed to be the photo-oxidation of uroporphyrinogen (a tetrapyrrole) by UVC, and this oxidation is accompanied by the release of molecular hydrogen. The oxidation of uroporphyrinogen to uroporphyrin, the first biogenetic porphyrin, could have occurred anaerobically and abiologically on the primordial Earth 3 billion years ago (Mercer-Smith et al., 1985). The indole structure can be found in many organic compounds, like the amino acid tryptophan, and in tryptophan-containing enzymes and receptors, alkaloids and pigments. The indole ring is electron rich and will lose an electron (oxidized) to an electrophilic compound, like a heavy metal, to decrease its oxidation number. The most reactive position on the indole structure for electrophilic aromatic substitution is C-3, which is $10^{13}$ times more reactive than benzene. Presently, cationic porphyrins are known to bind to the tryptophan moiety of proteins (Zhou et al., 2008). A similar situation to tryptophan occurs with chlorophyll, the light-capturing molecule of plants.

Photosynthesis

Most proteins are endowed with an intrinsic UV fluorescence because they contain aromatic amino acids, particularly phenylalanine, tyrosine and tryptophan. Comparing the three aromatic amino acids, tryptophan has the highest fluorescence quantum yield, overshadowing markedly the emissions of the other two. Generally, a distinction is made between tryptophan and non-tryptophan fluorescence. The tryptophan amino acid contains an indole backbone and absorbs light. Free tryptophan has characteristic fluorescence absorption at UVB (Borkman and Lerman, 1978; Lin and Sakmar, 1996), and the fluorescence emission is in the range of UVA-blue light (Du et al., 1998). This amino acid in proteins is needed for solar energy to drive photosynthesis in cyanobacteria, algae and plants (Vavilin et al., 1999). Solar energy conversion in photosynthesis involves electron transfer between an excited donor molecule and an acceptor molecule that are contained in the reaction center, an intrinsic membrane protein pigment complex (Wang et al., 2007). In the photosynthetic reaction centers of Rhodobacter sphaeroides, there are 39 tryptophan residues. Initiation of the electron...
transfer reaction by excitation results in a transient change in the absorbance at UVB, near the peak of the tryptophan absorbance band. According to Wang et al. (2007):

Given the similarity of the core features of the photosynthetic complexes from bacteria and plants, it is very likely that this same framework holds true for the initial electron transfer reaction of photosynthesis in general and possibly for other protein-mediated electron transfer reactions on similar time scales.

Absorption of blue light waves in chloroplasts leads to excitation of the indole structure of tryptophan so that it loses one of the electrons from its indole ring structure – it becomes oxidized. The electron that is lost from the indole ring passes through the intermediary of heavy metals to make its way down the electron chain. This process leads to the production of reducing cofactors such as nicotinamide adenine dinucleotide (NADH), or reduction of H₂O to O₂. In bacterial ferric cytochrome P-450, the initial event of photoreduction is the photo-ionization of tryptophan in the active site of P-450 (Pierre et al., 1982). A laser flash at 265 nm, near the UVB range, triggers the nanosecond event of a protein structural change coincident with an ejection of electrons, and is followed by the photoreduction of the heme moiety (Bazin et al., 1982). The transfer of electrons between tryptophan and the heavy metals occurs at extremely rapid rates of several nanoseconds (Shih et al., 2008). This process takes place during photosynthesis, and is the procedure that converts solar energy into biological energy. CO₂ and water are converted to O₂ and glucose. This is the most important biochemical process on Earth. The Earth’s atmosphere contains 20 percent oxygen, and drives the biological evolution of aerobic organisms. Photosynthesis occurs in certain bacteria (e.g., cyanobacteria), algae (e.g., green algae) and all plants (Bryant and Frigaard, 2006).

Chloroplasts

Plants evolved a specialized intracellular organelle, the chloroplast, not only to capture light, but also as the source of tryptophan synthesis. This organelle may have evolved from captured cyanobacteria, and contains several hundred copies of chlorophyll. Chlorophyll became the universal transformer of solar energy in bioenergetics, and is sensitive to both blue and red light. In addition to its role in photosynthesis, blue light absorbance has been implicated as an early step in certain blue light-mediated morphogenetic events (Rubinstein and Stern, 1991). The spectra for blue light-stimulated stomatal opening and phototropism are specialized for sensory transduction in the chloroplast (Quiñones et al., 1998). Thus blue light in plants not only underlies photosynthesis, it also produces morphological plasticity in the plant leaf to promote sensory transduction of light energy into bioenergy. Structural and functional advantages of the chlorophyll molecule may have determined its selection in evolution (Mauzerall, 1973). Chloroplast have a high need for tryptophan because of its light-absorption functions.

Amino acid

Tryptophan is the largest and most hydrophobic amino acid, and provides important folding signals to large proteins (Aoyagi et al., 2001). Tryptophan is the least used amino acid in the composition of protein molecules, generally comprising around 1–2 percent of the protein weight. In the basic genetic code, only one code is used for tryptophan, 'UGG', and this is flanked by stop codons on UAA, UAG, and UGA. Yet many important molecules are derived from tryptophan, including the nucleic acids adenosine and thymidine in DNA. Furthermore, a novel nucleolar protein, WDR55, carries a tryptophan–aspartate repeat motif and is involved in the production of ribosomal RNA (rRNA) (Iwami et al., 2008). These findings suggest that WDR55 is a nuclear modulator of rRNA synthesis, cell cycle progression, and embryonic organogenesis. Thus, despite its limited abundance, tryptophan and its associated molecules are involved in all cellular aspects of the organism’s life, and serve key regulatory roles in mitosis (Humphrey and Enoch, 1998), cell movement (Efimenko et al., 2006) and maturation (Cooke et al., 2002). The synthesis of tryptophan takes several key enzymes: anthranilate synthase (EC 4.1.3.27), anthranilate phosphoribosyl-transferase (EC 2.4.2.18), anthranilate phosphoribosyl-isomerase (EC 5.3.1.24), indole-3-glycerol-phosphate synthase (EC 4.1.1.4) and tryptophan synthase (EC 4.2.1.20) (Figure 2). These enzymes are found in primitive unicellular organisms and in all plant systems. In many organisms there are isoforms of these that provide redundancy in tryptophan synthesis. In plants, tryptophan biosynthetic enzymes are synthesized as higher molecular weight precursors and then imported into chloroplasts and processed into their mature active forms (Zhao and Last, 1995). Chloroplast organelles contain the genes and enzymes, similar to those seen in cyanobacteria, required for tryptophan synthesis. Despite the abundant amount of tryptophan made by lower organisms, animals are tryptophan autotrophs, which lack the genes necessary for tryptophan synthesis. Tryptophan for serotonin synthesis is obtained from food. Often the main source of food is proteins from other animals; despite the fact that the amount of tryptophan in protein from animal sources is the least compared to the other amino acids.
Tryptophan levels are much higher in fruits, vegetables and nuts. Once digested, tryptophan exists in a free and bound form in the plasma. Only the free form is available for transport into the brain, and its transport must compete with the uptake of all the other, more abundant, aromatic amino acids (e.g., tyrosine, phenylalanine, leucine, isoleucine, valine and methionine) (Curzon et al., 1973). The synthesis of serotonin in humans appears to be restricted to a few cell types (e.g., mast cells and neurons). Selected cells in all organs have specific uptake proteins for capturing serotonin from the plasma where it is stored. The importance of this will be discussed later.

The capture of light by tryptophan is used at the active site by nearly all proteins (e.g., chlorophyll, rhodopsin and skin pigment cells) which capture light (Angiolillo and Vanderkooi, 1996). A long-range transfer of electrons to cytochromes from tryptophan can be demonstrated with a number of proteins, including paralbumin, aldolase and

![Diagram of the synthesis of tryptophan from chorismate]

Figure 2 The five enzymatic steps in the synthesis of tryptophan from chorismate; the names of each are provided in the text. In plants, these enzymes and the chloroplast genes for them are located within the chloroplast. In animals, the genes are inactive and all tryptophan is obtained from external sources.
liver alcohol dehydrogenase (Dadak et al., 1992). Thus, tryptophan is very sensitive to light in a variety of protein environments, and readily releases its electrons from the excited triplet state upon light exposure. This ability to transfer electrons is not only utilized in the initial events of photosynthesis. In the light receptor rhodopsin, there is rotation of a single tryptophan molecule when meta I is converted to meta II after illumination (Chabre and Breton, 1979). Photoactivation of rhodopsin involves a change in the relative disposition of transmembrane helices 3 and 6, which contain Trp126 and Trp265 respectively, within the receptor (Lin and Sakmar, 1996). These studies show that tryptophan serves key photo-signaling properties in light receptor rhodopsin, probably the most primitive of all G-protein receptors.

Tryptophan’s ability to absorb UV light can be put to advantage. The bacterium Bacillus subtilis is protected from the lethal actions of ultraviolet radiation by tryptophan (Hunt, 1964). UV and X-ray light produce lumi

nescence of tryptophan (Steen, 1967). This absorption provides protection by filtering harmful UV light before it can reach the underlying DNA and photoreceptors. The UV absorbance in chicken eye aqueous is partially accounted for by the presence of tryptophan (Ringvold et al., 2000).

Tryptophan has many functions in the cells, not only as an essential amino acid and chromophore but also because it makes niacin and all its precursors. NAD+ and NADP+ cofactors are involved in nearly all aspects of cell metabolism (Cox et al., 2000). De novo synthesis of nicotinamide adenine dinucleotides from tryptophan is a more important source of these coenzymes than is the utilization of dietary nicotinamide or nicotinic acid (Bender and Olufunwa, 1988). In the nucleus, niacin is important for DNA repair, and tryptophan capture of light appears to be responsible for the DNA photo-damage associated with mutation and cell death in the absence of repair (Friedberg et al., 1995).

**Tryptophan derivatives**

Photosynthesis is a major risk to cells as well as nutritional benefits. Photosynthesis can be perturbed by upsetting the balance between the rates of light collection and light use, resulting in the production of reactive oxygen species (ROS) (Asada, 1996). Left unchecked, ROS are damaging to protein function and membrane integrity, and pose a serious threat to photosynthetic organisms. UV light reaction with tryptophan generates many photo-products having deleterious actions. UVB radiation of N-formylkynurenine generates free radicals such as singlet oxygen and superoxide (Grossweiner, 1984). Tryptophan also generates fluorescent photoproducts which inhibit the growth and differentiation of cultured fertilized sea urchin eggs and mouse fibroblasts (Zigman and Hare, 1976). Thus a wide range of cells, from bacteria to mammals, are harmed by photo-oxidized tryptophan. The damage done to the human skin by sunlight can be largely attributed to the actions of tryptophan metabolism via the pyrrolase, kynureninidine and niacin pathways (Binazzi and Calandra, 1975). Ultraviolet light sensitizes tryptophan to enhance the photooxidation of tyrosine to dopachrome, a precursor of melanin (Badu and Joshi, 1992).

The critical problem in oxygen generating cells was what to do with all the reactive oxidizing chemicals produced during the generation of oxygen. Many of the derivatives of tryptophan evolved to function as antioxidant molecules in simple cells long before they assumed more complex functions in animals and humans. Substituted indoles are derivatives of the tryptophan-based tryptamine alkaloids, such as serotonin, melatonin and auxin; the hallucinogens psilocybin, DMT, 5-MeO-DMT; and the ergots, such as ergotamine and LSD (Schultes and Hofmann, 1973). N-formylkynurenine, 5-methoxytryp

amine, auxin and melatonin in prokaryotes function as photosensors, antioxidants and pattern generators for flagella movement, and in defense mechanisms. The defense mechanism may involve attack of plants by fungi, and a role for the phytohormone indole-3-acetic acid or a structurally related compound. Many of these products also have morphogenic actions and play a role in both apoptosis and mitosis. Many of the alkaloids produced from tryptophan have powerful actions on the human brain by acting mainly through the serotonin receptors. The structures of some of these compounds are shown in Figure 3.

Melatonin is a powerful antioxidant (Hardeland, 2005). Melatonin is found in all plants and animals, including algae. Melatonin has been shown to inhibit microtubule function in flagella and in mitosis. Melatonin synthesis has a diurnal rhythm in many protists and plants. It functions as an antioxidant in plants. Seasonal animals use melatonin as a biological signal for the organization of day-length dependent (photoperiodic) annual functions such as reproduction, behavior, coat growth and camouflage coloring (Chaturvedi, 1984). Melatonin is also related to the mechanism by which some amphibians and reptiles change the color of their skin, and, indeed, it was in this connection that the substance was first discovered (Sugden et al., 2004).

AUXIN (hydroxyindole acetic acid) is a protective, antioxidant compound found in unicellular organisms (Cooke et al., 2002). Auxin is an important phototrophic hormone in plants, is present in bacteria, and functions to stimulate growth and survival. It has many different effects, such as inducing cell elongation and cell division, with
all the subsequent results for plant growth and development (Stern et al., 2002; Mauseth, 2008). Auxin has been reported in several bacteria, and the key enzyme in the auxin synthetic pathway was found in the genome sequence database of Paenibacillus polymyxa (Phi et al., 2008). On the cellular level, auxin is essential for cell growth, affecting both cell division and cellular expansion (Perrot-Rechenmann et al., 2002). Depending on the specific tissue, auxin may promote axial elongation (as in shoots), lateral expansion (as in root swelling) or isodiametric expansion (as in fruit growth). Growth and division of plant cells together result in growth of tissue, and specific tissue growth contributes to the development of plant organs. Growth of cells contributes to the plant’s size, but uneven localized growth produces bending, turning and orientation of organs — for example, stems turning toward light sources (phototropism), roots growing in response to gravity (gravitropism), and other tropisms. Auxin controls the orientation of cortical microtubules in maize, perhaps caused by a reduced microtubule turnover (Wiesler et al., 2002). Actin transport is essential for its uneven distribution in plants. Auxin transport inhibitors impair vesicle motility and actin cytoskeleton dynamics in yeast, plants and animals (Dhonukshe et al., 2008). In plants, auxin is synthesized in specialized cells and is transported throughout the plant to influence leaf and root growth. Its specific function in leaves is to move the entire photo-generating organ towards the source of solar energy.

N-formylkynurenine functions as a photosensitizer, and is made in mitochondria by the oxidation of tryptophan (Møller and Kristensen, 2006). 5-Methoxytryptamine is also found in nearly all living organism, and is a key intermediate in the pineal synthesis of melatonin in vertebrates. The production of all other 5-methoxyindoles in the pineal gland as well as in the retina is always larger than that of melatonin. In the pineal gland, 5-methoxytryptophan, for example, is synthesized in a quantity which is 60 to 170

Figure 3 Many of the alkaloid compounds derived from the tryptophan. Some of these compounds, such as auxin, DMT and melatonin, appear to have been made in protista, occurring before plants. Some of these compounds are known to be potent hallucinogens when ingested by humans (see text). It is reported that serotonin is found in the Fungi Kingdom in yeast cells.
times greater than that of melatonin, while in the retina the synthesized amount of 5-methoxytryptophan is even 60 to 1000 times greater than that of melatonin (Pévet et al., 1981). This would provide a pathway for the synthesis of melatonin independent of one using 5-hydroxytriptamine, or serotonin.

Below is a list of some of the natural psychoactive drugs synthesized from tryptophan. All these compounds can function as antioxidants in single-cell organisms, and many have been used by man as entactogens and ethereogens for thousands of years.

1. Psilocybin mushrooms (also called psilocybian mushrooms): these are fungi. Kingdom Fungi includes yeasts, rusts, smuts, molds, mushrooms and mildews. Though formerly classified as plants, fungi lack chlorophyll and the organized plant structures of stems, roots and leaves.
2. Dimethyltryptamine (DMT): this occurs in many species of plants, and is commonly used as an hallucinogen via drinking or smoking.
3. Bufotenine: this molecule is found in mushrooms, plants, and the skin and venom of toads (Bufo genus).
4. 5-MeO-DMT: this molecule is widely distributed in plants and toads.
5. Ergot, ergotamine: the parent compound of the major hallucinogen LSD has long been known to be produced by a fungus, genus Claviceps. The hallucinogen was synthesized by the addition of diethylamine to ergotamine by the chemist Albert Hofmann at the Sandoz Laboratory. LSD is believed to be one of the most potent mind-altering compounds discovered to date.
6. Ibogaine: this is found in a number of plants, principally in a member of the dogbane family known as iboga (Tabernanthe iboga).
7. Yohimbine: this is the principal alkaloid of the bark of the West-African evergreen Pausinystalia yohimbe Pierre. In Africa, yohimbine has traditionally been used as an aphrodisiac.

Serotonin

**Biosynthesis**

Serotonin is synthesized from tryptophan by two enzymes: tryptophan hydroxylase, which requires molecular oxygen; and tetrahydro-biopterin and aromatic amino-acid decarboxylase, which requires pyridoxal phosphate (Figure 4). It is principally metabolized by monoamine oxidase (A & B) to generate H₂O₂ and 5-hydroxyindole acetic acid. MAO A & B have been detected in Fungi (Sabin et al., 1998). In the pineal gland of vertebrates, serotonin is methylated to produce melatonin. Precursors of these four enzymes (hydroxylase, decarboxylase, oxidase and methylase) are found in four major kingdoms of life (Bacteria, Fungi, Plant, and Animal).

**Primitive hydroxylase enzymes**

One of the solutions for removing excess O₂, and the potent threat of excess oxidation in cells, is to use the biological machinery that evolved to deal with CO₂. Anaerobic cells had developed a variety of enzymes for converting CO₂ into biological energy in the form of...
glucose, with $O_2$ as a byproduct. The most common process was to produce the sugar, glyceraldehyde-3 phosphate, a three-carbon sugar produced by three molecules of $CO_2$. The first enzymatic step in this reaction involves the attachment of a molecule of $CO_2$ to the five-carbon sugar, ribulose bisphosphate (RuBP). This step is emphasized because the enzyme that catalyzes this initial reaction, and possibly the most abundant enzyme on Earth, is RuBP carboxylase, also known as rubisco. In the very early stages of life on Earth, the carboxylase primarily attached to $CO_2$; however, as $O_2$ levels increased it was shown that this compound could react more favorably with oxygen (Smith, 1976). The oxygen-based reaction is energy inefficient, but serves to remove excess oxygen during periods of high light flux. This may have been the first enzyme to attach oxygen to a substrate (such as tryptophan) to produce 5-hydroxytryptophan (5-HTP). This enzyme is called a hydroxylase because only a single oxygen is used and the other forms water. RuBP carboxylase has the same phosphate-binding site sequence found in tryptophan biosynthetic enzymes (Wilman, 1991).

Phenylalanine biosynthesis evolved prior to the addition of branches leading to tyrosine and tryptophan. An evolutionary scenario has been developed that begins with non-enzymatic reactions which may have operated in primitive systems, followed by the evolution of an enzymatic system that pre-dated the divergence of major lineages of modern bacteria (Gram-positive bacteria, Gram-negative purple bacteria, and cyanobacteria) (Ahmad and Jensen, 1998). The bacteria (Chromobacterium violaceum) enzyme phenylalanine hydroxylase contains copper ion, and if the enzyme is oxidized it is inactive (electron acceptor, gives up a hydrogen molecule); a single hydrogen ion (H$^+$) is sufficient to reduce the enzyme to a catalytically active state (Pember et al., 1986). H$_2$-bioperin reductively activates the enzyme (donates electron). Bacteria (Pseudomonas fluorescens) contain a primitive bioperin hydroxylase, cyanide oxygenase, which can convert KCN to $CO_2$ (Kunz et al., 2001). Many of these enzymatic properties and the use of bioperin cofactor are shared by the mammalian tryptophan hydroxylase, which is the rate-limiting step for serotonin biosynthesis.

The substrates for the primitive hydroxylase enzyme were tryptophan, tyrosine and phenylalanine, all of which can capture light (Grenett et al., 1987; Boularand et al., 1998; Wiens et al., 1998). The hydroxylase enzyme gave rise to a very large number of complex alkaloids in plants, all of which are potent antioxidants in their own right. As we now know, cellular oxidation is important for cell maturation and division, but excess oxidation results in cell death. The synthesis of pharmaceutically important indoles involves the hydroxylase as well as decarboxylase enzymes (Facchinetti et al., 2000). 5-HTP, the immediate precursor of serotonin, is formed from tryptophan hydroxylase. This molecule is rapidly converted to serotonin by the ubiquitous carboxylase working in reverse to function as a decarboxylase. Thus, serotonin is produced from tryptophan by enzymes commonly used in anaerobic organisms before $O_2$ was formed inside cells. Besides the algae, fungi and molds, the most efficient generators of $O_2$ and serotonin are plants.

Decarboxylase

The second enzyme in serotonin biosynthesis is tryptophan decarboxylase. The bacteria, Enterobacteria cloaceae strains that are normally associated with plant roots, produce auxin by using the enzyme indolepyruvate decarboxylase (Zimmer et al., 1994). Aromatic L-amino acid decarboxylase occurs in plants (Facchinetti et al., 2000). For example, tryptophan decarboxylase in plants leads to the biosynthesis of pharmaceutically active indole alkaloids. These compounds are abundant throughout the plant kingdom, and are known to produce strong psychic or hallucinogenic responses in humans (see Figure 3). In animals, this enzymes losses its specificity for tryptophan and becomes a general aromatic acid decarboxylase. It is likely that as animal cells had a marked reduction in tryptophan due to loss of tryptophan synthesizing enzymes, there was less evolutionary need for a specific tryptophan decarboxylase enzyme.

Cofactors

Tryptophan is necessary for the synthesis of a variety of cofactors, including bioperin, NADH and pyridoxal phosphate (Nelson and Cox, 2008). Bioperin is an essential cofactor in hydroxylase enzymes, and is necessary for the synthesis of serotonin. NADH and NADPH are involved in nearly every redox reaction in all living cells. They act as both oxidizing and reducing agents. Pyridoxal-5’-phosphate is a catalysis (redox) partner in a variety of reactions involving amino acids (Alexander et al., 1994). Pyridoxal phosphate, the decarboxylase cofactor, in the form of an adduct absorbing at 330–340nm, is suggested as a candidate for photoactivation of the 5-hydroxytryptophan decarboxylation for the role of the photoactive chromophore of decarboxylase. The cofactor pyridoxal-5-phosphate appears to have emerged very early in biological evolution; conceivably, organic cofactors and metal ions were the first biological catalysts (Mehta and Christen, 2005).

Presence of serotonin

In prokaryotes and algae living under anaerobic or aerobic conditions, the evidence for the presence of serotonin
is weak, although all serotonin biosynthetic enzymes and cofactors are present. The enzymes aromatic amino acid (tryptophan) hydroxylase, tryptophan (aromatic amino-acid) decarboxylase, monoamine oxidase and aromatic hydroxylase are conserved in unicellular organisms. The compounds produced by these enzymes all have roles in light-induced reactions involved in regulating the oxidative reactions in cells. In nearly every unicellular organism, tryptophan and its metabolites (auxin, melatonin and 5-methoxytryptamine) function as light sensors (needed for diurnal rhythms) and as antioxidants. Melatonin and 5-methoxytryptamine appear to be ubiquitous substances found in nearly every living cell (Hardeland, 1999). Auxin is also found in many unicellular organisms (Overbeek, 1940; Jacobs et al., 1985). In fungi, Candida guilliermondii, serotonin (and other hydroxylated tryptamines) and ergot derivatives provide protection from UV toxicity and stimulate cell proliferation (Strakhovskaia et al., 1983; Belenikina et al., 1991). Candida cannot make oxygen, but depends on oxygen for energy production (obligate aerobes).

The Plant Kingdom

In plants, the synthesis of serotonin is much higher than in mammals (Garattini and Valzelli, 1965; Smith, 1971; Sparks and Slevin, 1985). The explanation for the high levels of serotonin is abundance of intracellular oxygen, tryptophan, and the enzymes and cofactors necessary for the production of 5-hydroxytryptophan. The levels of serotonin inside plants far exceed those seen in the animal brain, by approximately 100-fold – for example, banana skin has a level of 40 mg/g, while rat hippocampus has a level of 0.4 mg/g. Interestingly, the immediate precursor of 5-HT, 5-HTP, accounts for 20 percent of the total fresh weight in seeds from Grivonia simplicifolia, a tropical shrub of west Africa, which has potent medicinal properties (Lemaire and Adosraku, 2002). This seed has 500 times the serotonin levels measured in mammalian brains, where 5-HTP levels are almost undetectable.

The hydroxylase enzyme is of double significance in plants, since not only is molecular oxygen removed from the cell but also a very reactive antioxidant molecule is produced. Serotonin also provides a source for auxin and other important alkaloid production in plants. Despite the high levels of serotonin in plants, most general botany textbooks say nothing on this topic.

The Animal Kingdom (Table 2)

Animal cells lack chloroplasts, which are organelles central to plant photosynthesis and tryptophan synthesis (Table 2). This lack of a key evolutionary mechanism of life led animals to develop a number of traits in order to survive. Animals acquire photosynthesis-produced carbon by forming symbioses with algae and cyanobacteria. These associations are widespread in the phyla Porifera (e.g., sponges) and Cnidaria (e.g., corals, hydra), but are otherwise uncommon or absent from animal phyla (Venn et al., 2008). The sponges (Porifera), the most primitive animal form, evolved about 600 million years ago (Valentine, 2004). Animals had to move to capture organisms that contained tryptophan, and to breathe to extract O₂ from the atmosphere. 5-HT- and 5-hydroxytryptamine-derived alkaloids are found in sponges (Salmoun et al., 2002). This species does not have a nervous system, and feeds by filtration. In hydra, the most primitive animal with a specialized nervous and motor system, 5-HT appears to be localized to sensory cells scattered along the epithelium of the organism. When a distinct nervous system is seen, such as in the flatworm (Stenostomum leucopus), serotonin neurons are localized there (Wikgren and Reuter, 1985). Serotonin in animals is produced in very low quantities because of the scarcity of tryptophan, and this may explain the few cells that contain 5-HT. As seen in hydra, these specialized 5-HT cells are nevertheless ideally localized, and have pronounced actions on the life of the organism (Figure 5).

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Age (Mya)²</th>
<th>Class, genus, species, common names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porifera</td>
<td>600</td>
<td>Sponge</td>
</tr>
<tr>
<td>Cnidaria</td>
<td>600</td>
<td>Coelenterates; coral, hydra</td>
</tr>
<tr>
<td>Annelida</td>
<td>525</td>
<td>Earthworm</td>
</tr>
<tr>
<td>Echinodermata</td>
<td>500</td>
<td>Sea urchins</td>
</tr>
<tr>
<td>Molluska</td>
<td>450</td>
<td>Gastropoda; alysia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cephalopoda; squid</td>
</tr>
<tr>
<td>Anthropoda</td>
<td>400</td>
<td>Crustacean; lobster</td>
</tr>
<tr>
<td>Arthropoda</td>
<td>350</td>
<td>Insecta; drosophila</td>
</tr>
<tr>
<td>Nematoda</td>
<td>325</td>
<td>C. elegans</td>
</tr>
<tr>
<td>Chordata</td>
<td>400</td>
<td>Vertebrate: subphylum</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>Fish</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>Reptiles</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>Amphibians, Newt</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Birds</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>Mammal</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>Homo sapiens</td>
</tr>
</tbody>
</table>

Table 2: The Metazoa (Animal Kingdom), a major subdivision of life that includes all animals¹

Source: University of California Museum of Paleontology (ucmp.berkeley.edu/index.php).

¹Fossil records indicate that most metazoan phyla developed during the Cambrian explosion (542–488 million years ago). Many of the classes of vertebrates have fossil records indicating their appearance after this time.

²Mya, million years ago.

Figure 5: Evolution of Serotonin: Sunlight to Suicide
As these organisms have evolved a neuronal center for responding to their complex environment, serotonin continues to position itself to interact maximally with organizing centers. In aplysia there is a primitive brain, and from the very beginning serotonin is present. According to Marois and Carew (1997):

The results indicate that the first serotonergic cells emerge at mid-embryogenesis and that a total of five cells make up the entire serotonergic system by hatching. The primitive serotonergic cells in aplysia are part of a newly discovered ganglion in aplysia, called the apical ganglion.

The 5-HT neuronal distribution is described in adult aplysia, and the vast serotonergic neuronal distribution through the nervous system, gut and periphery is notable (Goldstein et al., 1984):

Many neuronal cell bodies are stained in addition to the giant cerebral neuron of the cerebral ganglion and cells in the RB cluster of the abdominal ganglia which previously had been characterized biochemically and pharmacologically as being serotonergic. Neuronal cell bodies, both in central ganglia and in the wall of the gut, are encircled by plexuses of serotonergic varicosities. The neuropil of ganglia and the eye also contain fine, immunoreactive axons bearing varicosities. Intranganglionic connectives and nerves contain many stout fluorescent axons. Serotonergic varicosities are also observed in the connective tissue sheath surrounding central ganglia and nerves, as well as in heart and body muscle, blood vessels and gut.

The extensive distribution of serotonergic neurons in lower animals besides the brain and gut is not seen in mammals. The serotonergic neurons are located in the midbrain reticular formation, and have extensive axonal branching throughout the neuroaxis (Azmitia and Segal, 1978; Azmitia and Gannon, 1983) and the gut enterochromaffin cells and myenteric plexus (Gershon and Tack, 2007). Serotonergic axons from the myenteric plexus can innervate the nearby pancreas (Kirchgessner and Gershon, 1990). Mast cells located throughout the body and lying near blood vessels are the principal source of tryptophan hydroxylase in most peripheral tissues. These neuroendocrine mast cells contain serotonin at early gestational stages, and are positioned to serve a trophic function throughout the body as described for auxin in plants (Cutz, 1982).

In the brain of animals, the serotonin system has undergone considerable modification to keep abreast of the increased size and complexity of the brain (Figure 6). The neurons in the brains which contain serotonin actually decrease in relative size as one ascends from aplysia to primates. In lower organisms single serotonin neurons can regulate particular circuits, while in rodents the serotonergic neurons appear to act as large clusters of neurons acting together to influence general brain circuits. Finally, in primates the distribution of neurons in the raphe midbrain becomes more clustered, and these smaller groups send axons, often myelinated, to specific regions of cortex. This final arrangement allows serotonin to participate in multiple, discrete cortical functions than are not possible in lower mammals. The morphological organization appears to be continually evolving, and may enable more precise distribution of serotonin within the brain of humans.

Receptors

Capturing light is one of the most primitive functions of a receptor. Primitive rhodopsin GTP-linked receptors, which
years ago. If rhodopsin is considered the prototype of the 5-HT$_{1A}$ receptor, the emergence of serotonin receptors occurred 3.5 to 2.5 million years ago in cyanobacteria.

Life began in sea water, where Na$^+$ and Cl$^-$ ions are highly concentrated. Cells evolved a mechanism to exclude these ions in order to maintain a stable membrane potential, and ‘neurotransmitters’ evolved the ability to regulate these specific ion channels to rapidly manipulate the membrane potential. Second messengers, e.g., G proteins, c-AMP, and phospholipase C systems, appeared early in evolution and occur in all phyla that have been investigated. With the possible exception of the Porifera and Cnidaria, all the classical ‘neurotransmitter’ receptor subtypes identified in mammals occur throughout the animal phyla (see Walker et al., 1996). Many of the serotonin receptors are seen in the embryonic stage – for example, H$^+$–5-HT binding is seen in the blastula and gastrula of sea urchins (Brown and Shaver, 1989). A gene from the sea urchin encoding the serotonin receptor (5-HT–hpr) was identified and showed sequence homology with the aplysia 5-HT$_3$ receptor (Katow et al., 2004). Cells expressing the 5-HT receptor appeared near the tip of the archenteron in 33-h post-fertilization larvae. The serotonergic receptor cells developed 7 cellular tracts by 48 hours, and extended short fibers to the larval body surface through the ectoderm. These serotonergic receptor cells are a mesencephalic cell lineage, which appear to transmit serotonin signals to ectodermal cells at the start of gastrulation in sea urchins. In humans, the 5-HT$_{1A}$ receptors are at their highest levels before birth (Bar-Peled et al., 1991). In rats, the receptors for serotonin are not only present in the fetus, but can also be modified by injections of agonist (Whitaker-Azmitia et al., 1987). All the invertebrate receptors so far cloned show homologies with mammalian receptors. This indicates that many of the basic serotonin receptor subtypes evolved during early geological periods and appeared at early ontogenic times. As the saying goes, ‘Ontogeny recapitulates Phylogeny’.

Tremendous diversity has occurred in receptors in mammals. There are hundreds of serotonin receptor clones, and the human brain has at least 20 separate neuronal transcripts of 5-HT receptors (Moroz et al., 2006). Serotonin is specifically bound to at least 16 specific receptor proteins in the human brain which regulate ion channels, c-AMP levels and kinase activity in neurons. The 5-HT receptors are found in every cell of the body. Why so many, and why such a large distribution? It can be speculated that the difficulty in making and obtaining tryptophan in animals results in low serotonin availability. The function of a receptor is to alert a cell that a chemical is present in the environment, without removing or altering the chemical. Thus, if a chemical is in short supply, the appearance of receptor molecules permits its actions

![Figure 6](image-url)
to be transmitted throughout the organism. In order for this to be maximally effective, an efficient mechanism for the distribution of serotonin is required. Animals have specific tryptophan and serotonin binding proteins in their blood to help transport these molecules to specific target areas, such as the brain. Glial cells at the junction of the blood–brain barrier have special transport proteins for concentrating tryptophan and delivering it to the serotonin neurons (Bachmann, 2002; O’Kane and Hawkins, 2003). Serotonergic neurons developed long, unmyelinated axons that can take up tryptophan and utilize enzymes required for serotonin synthesis throughout the brain and gut. In summary, loss of tryptophan has promoted a highly branched, unmyelinated neural network, and a plethora of specific receptors to maximize serotonin’s actions.

**5-HT function**

Plants do not have neurons or muscles, but they are nevertheless capable of limited movement by rotating their leaves towards the light and sending their roots deep into the soil to capture $H_2O$ and nitrogen. In multicellular plant organisms, growth and mitosis are similar to that seen in unicellular organisms and fungi (Eckert, 1972; Weiger, 1997). In lower animals, serotonin neurons are primarily sensory neurons (activated by external stimuli), and influence food intake, defense withdrawal, and complex locomotor actions such as swimming (e.g., in sea urchins, Echinodermata) (Yaguchi and Katow, 2003). In the worm ganglia (Annelids), serotonin is first found in interneurons, which permits better regulation of complex behaviors such as swimming (Kristan and Nusbaum, 1982) and possibly learning and memory (Moss et al., 2005). In *Caenorhabditis elegans* (Nematodes), 5-HT is involved in modulating feeding behavior by rapidly altering a chemosensory circuit (Chao et al., 2004). The involvement of serotonin is also directed at neurons. The serotonin released from an apical ganglion interacts with specific neuronal receptors to increase or decrease the firing rate of its target cells involved in sensory and motor processing (Marois and Carew, 1997). Actions of serotonin on sexual activity and reproduction are evident (Boyle and Yoshino, 2005). In addition, serotonin changes cAMP and $Ca^{2+}$ levels in its target neurons, influences their transcription rate and modifies cell morphology (Pettigrew et al., 2005).

The actions of serotonin thus extend from that of antioxidant through morphogenesis and ascend to being involved in complex behaviors such as an organism’s position in a social hierarchy. Serotonin in lobsters (Arthropods) regulates socially relevant behaviors such as dominance-type posture, offensive tail flicks, and escape responses (Kravitz, 2000). This action of serotonin may be through the $5-HT_{1A}$ receptor (Sosa et al., 2004). 5-HT-regulated social and mental behaviors increased in number and complexity as these functions became more advanced and complicated. The many reports of increased social dominance in primates (Edwards and Kravitz, 1997) and improved mood and confidence in social interactions in humans after using drugs which increase serotonin levels are well documented (Kramer, 1993; Young and Leyton, 2002). In these higher animals, 5-HT continues in its role of a homeostatic regulator in adjusting the dynamic interactions of these many functions within the organism, and how the organism interacts with the outside world.

**Trophic**

The actions of serotonin in Metazoa begin very early in development. They are seen at both the blastula and gastrula stages, as noted by the appearance of serotonin...
receptors in the blastula stages. In Mollusca, serotonin is involved in the determination of the animal pole during early blastula stages (Buznikov et al., 2003). Application of para-chlorophenylalanine (PCPA, a tryptophan hydroxylase inhibitor) interferes in morphogenesis by arresting gastrulation, which results in the disintegration of embryos. At lower concentrations of PCPA, retarded morphogenetic movements were observed that resulted in malformations in the anterior parts of the embryos and yolk granule degradation in the notochord (Hämäläinen and Kohonen, 1989). In mammals, the actions of serotonin on the developing fetus are felt from the time of conception due to the circulating serotonin in the plasma of the mother (Côté et al., 2007). Serotonin neurons are formed very early in gestation in vertebrates (Lidov and Molliver, 1982; Wallace and Lauder, 1983; Okado et al., 1989). Peripheral tissue also expresses cells which contain serotonin. For example, the mast cells (neuroendocrine) of the lung contain serotonin in the fetus (Kushnir-Sukhov et al., 2006). It is logical to assume that if serotonin made a very early phylogenetic appearance, then it should also make a very early ontogenic appearance. Plant seeds and animal embryos have the highest levels of serotonin.

By increasing cAMP and P-CREB, serotonin mediates a trophic response that may underlie both maturation and memory formation in aplysia (Glanzman et al., 1990). Thus, in much the same way as serotonin and its derivatives influence the process and organelles of photosynthesis to move in order to track the source of light, in animals serotonin influences the morphology of sensory and motor neurons involved in neuronal networking in order to track the source of relevant stimuli. The changes in neuronal morphology are particularly intriguing, because they affect neuronal connectivity in much the same way as has been proposed for vertebrates. Even a relatively brief removal of serotonin from the brain of vertebrates results in loss of spine, dendritic profiles and synapses (Yan et al., 1997; Okado et al., 2001). This topic of neuroplasticity has been extensively reviewed by the current authors (Azmitia, 2001, 2007; Azmitia and Whitaker-Azmitia, 1991, 1997; Jacobs and Azmitia, 1992).

In mammals, serotonin has evolved a trophic relationship with glial cells. High-affinity receptors have been identified on astrocytes and Schwann cells from rodents and primates (Hertz et al., 1984; Whitaker-Azmitia and Azmitia, 1986; Gaietta et al., 2003). One function is for astrocytes to provide serotonergic neurons with tryptophan (Pow and Cook, 1997). The serotonin receptors on astrocytes can also release the neurite extension factor S100B, and glucose (Azmitia, 2001). Serotonin application induces glial-derived neurotrophic factor (GDNF) mRNA expression via the activation of fibroblast growth factor receptor 2 (FGFR2) (Tsuchioka et al., 2008). Activation of serotonin receptors also promotes the development of glial cells in the brainstem of rats (Tajuddin et al., 2003).

The recruitment of secondary cells to amplify serotonin’s trophic actions emerged in animals. Astrocytes are found in vertebrates, and in C. elegans and drosophila. These supportive cells may have appeared even earlier. Using antibodies against a myelin marker and an astrocytic marker, evidence for glial cells was found in moths (Arthropoda) and aplysia (Roots, 1981). The emergence of these cells as targets for serotonin is what Brodie and Shore envisioned in 1957 when they termed the serotonin system the ‘trophotrophic system’. Serotonin has trophic functions (mitosis, apoptosis, differentiation and metabolism), directly and through astrocytes, the other major cellular system in the brain, by receptor-mediated changes in glucose availability and trophic factor release. These actions are considered to be significant in the development and aging of the brain (Azmitia, 1999). Serotonin can in fact be considered to be important for the development and maturation of the entire organism, since serotonin and its receptors are found throughout the body – see Hansen and Witte, 2008 (gut), Wasserman, 1980 (lung), Raymond et al., 1993 (kidney), Hagmann et al., 1992 (liver) and Nordlind et al., 2008 (skin).

The idea that serotonin functions as a trophic factor in vertebrate brains requires a new concept for how serotonin can be most efficiently distributed from axons. Traditionally, neurotransmitters are transported by the axon to a specific synaptic site where the neurotransmitter is released. This is seen for a proportion of the serotonin axons (Muller et al., 2007). There were major discussions regarding whether serotonin could also function by diffusion from unmyelinated axonal varicosities on to non-synaptic sites (Beaudet and Descaries, 1978), and the controversy was settled by accepting the idea of diffuse release, as well as acknowledging that many of the receptor targets of serotonin are on non-neuronal cells. For example, in the rat brain, serotonin axons course through the lateral and III ventricles along ependymal cells (Mollgård and Wiklund, 1979). Serotonin fibers can be considered to be a ‘drip irrigation system’ for the brain. As long as the axons are intact, serotonin is efficiently released throughout the brain. In old age and in neurodegenerative diseases, serotonin axons in the human brain degenerate (Azmitia and Nixon, 2008).

Seasonal affective disorder and suicides
Dysfunctions in brain serotonin are implicated in many mental disorders, such as autism, Down’s syndrome, anorexia nervosa, anxiety and depression. There are nearly 10,000 papers dealing with serotonin and various diseases ranging from alcohol addiction (Martinez et al., 2008) to herpes zoster (Ohyama et al., 2004). The relationship
between serotonin and depression is cited in over 13,000 papers, with 1750 citations since 2007. Furthermore, a strong correlation exists between brain serotonin levels, depression and suicide, with the first paper in this area written over 40 years ago (Shaw et al., 1967). Those attempting suicide had significantly lower levels of 5-HIAA in the CSF compared to controls (Mann et al., 1996). PET studies indicate that the 5-HT2A receptor is altered in depressed suicide attempters (Audenaert et al., 2006). A decrease in serotonin has serious consequences on normal brain homeostasis, both structural and functional, and influences a person’s desire to continue living. It is surprising to learn that sunlight has dramatic actions on the brain serotonin system of humans.

A seasonal variation in affective disorders was reported several decades ago (Videbech, 1975), and has certainly been noted from the earliest times of recorded history. All Northern hemispheric cultures since the Mesopotamians have developed special holidays to mark the nadir of light on Earth, and celebrations to counter winter’s gloom (for example, Makar, Sankranti, Saturnalia, and Dong Zhi) (Count and Count, 2000). Seasonal affective disorder (SAD) consists of recurrent major depressive episodes in the fall/winter with remissions in spring/summer, and is effectively treated with serotonin drugs and/or light therapy (Westrin and Lam, 2007). Treatment with light therapy or antidepressant medication is associated with equivalent marked improvement in the assessment of psychosocial functioning and life quality. There was no significant difference in measures in 96 SAD patients receiving 8 weeks of treatment with either (1) 10,000-lux light treatment and a placebo capsule, or (2) 100-lux light treatment (placebo light) and 20 mg fluoxetine (Michalak et al., 1992). Several studies have confirmed that patients respond favorable to light therapy (Yerevanian et al., 1986; Stewart et al., 1991; Rao et al., 1992).

Light therapy has effects on serotonin parameters in humans. It has been shown that blood serotonin increases in healthy subjects and patients with non-seasonal depression after repeated visible light exposure. Blood samples from jugular veins in 101 healthy men showed that turnover of serotonin by the brain was lowest in winter, and directly related to the prevailing duration of bright sunlight (Lambert et al., 2002). The production of serotonin measured by this procedure increased rapidly with exposure to increased luminosity. Serotonin levels were higher on bright days no matter what the time of year, and the amount of serotonin present reflected the hours of sun exposure on a particular day – conditions the day before had no effect. In a group of patients with a history of SAD, significantly lower plasma bioperin and tryptophan levels were measured that increased after light therapy (Hoekstra et al., 2003).

A seasonal rhythm in plasma serotonin transporter in normal subjects was first demonstrated over 25 years ago (Whitaker et al., 1984). There was a significant reduction in the Hamilton Depression Rating Scale (HAMD) score after therapy vs before treatment, and the Kd for citalopram binding was significantly higher after phototherapy than before treatment (Swiecicki et al., 2005). In agreement with the previous work, binding studies of 5-HTT show that this protein is in a sensitized state during depression in SAD, and normalizes after light therapy and in natural summer remission (Willeit et al., 2008). Phototherapy had a significant influence on both the measured serotonin transport parameters (Bmax and Kd).

This suggests that daily light therapy has a sound basis in biology and makes evolutionary sense.

Blue light is effective at increasing tryptophan absorption during photosynthesis in chloroplasts, and this light is efficient at treating patients suffering from SAD. As mentioned with the plant chloroplast system, it appears in human studies that blue light might be the most effective. Blue light can suppress melatonin levels and aid in circadian phase shift. Light therapy is effective at significantly reducing Hamilton Depression Rating Scale (SAD Version) when a narrow band of blue light (468 nm) is used (Glickman et al., 2006). The UV-A spectrum does not increase the antidepressant response of light therapy, and clinical application of light therapy should use light sources that have the UV spectrum filtered (Lam et al., 1992). Light therapy relieves suicidal ideation in patients with SAD consistent with overall clinical improvement. Emergence of suicidal ideas or behaviors is very uncommon with light therapy (Lam et al., 2000). It has been proposed that the lighting standards in the home and workplace should be re-evaluated on the basis of new knowledge regarding the neurobiological effects of light (Jacobsen et al., 1987). This might be considered one of the first steps taken by a society to achieve conditions conducive to enhancing serotonin function in the general population, and an acknowledgement of serotonin’s special relationship with sunlight that began to emerge at the beginning of life on Earth (Figure 7).

Summary

Sunlight has beneficial effects on the serotonin system and the mood and stability of humans. This is consistent with the idea that serotonin is involved in homeostasis in humans (Azmitia, 2001) and contributes to the emergence of mind (Azmitia, 2007). What is surprising is the consistency of serotonin’s function throughout evolution. The indole ring of tryptophan was the first and principal
Evolution of Serotonin: Sunlight to Suicide

and suicidal ideation can be treated with light therapy, which is intended to mimic the beneficial effects of natural sunlight. This chapter has followed an evolutionary path from tryptophan absorption of light in photosynthesis to serotonin’s actions in treating seasonal affective disorder. All cells and organs of the body, and especially of the brain, are affected by the serotonin system. The actions of sunlight may be the magic elixir to help maintain homeostasis between body and mind, improve social interactions, and create harmony among the phyla.

Acknowledgements

I am indebted to Dr. Patricia Whitaker-Azmitia for her comments during the preparation of this manuscript. I also acknowledge the many serotonin researchers whose work has inspired me to focus my career on a single brain chemical. Funding for this research was provided by a New York University Challenge grant.

References

18 Functional Anatomy of the Serotonergic System


Lidov, H.G. and Muller, M.E. (1982) An immunohistochemical study of serotonin neuron development in the...
20 Functional Anatomy of the Serotonergic System

Evolution of Serotonin: Sunlight to Suicide


22 Functional Anatomy of the Serotonergic System


