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Review

The role of serotonin in adult hippocampal neurogenesis

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HIGHLIGHTS

- Serotonin is a crucial monoamine in regulating adult hippocampal neurogenesis.
- Acute manipulation has long-term effects with distinctive actions of 5-HT receptors.
- Genetically modified animals reveal conflicting results on serotonins modulatory role.
- Serotonin mediates the pro-proliferative effect of running.
- Serotonin is pharmacologically relevant by mediating antidepressant response.

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ABSTRACT

Serotonin is probably best known for its role in conveying a sense of contentedness and happiness. It is one of the most unique and pharmacologically complex monoamines in both the peripheral and central nervous system (CNS). Serotonin has become in focus of interest for the treatment of depression with multiple serotonin-mimetic and modulators of adult neurogenesis used clinically. Here we will take a broad view of serotonin from development to its physiological role as a neurotransmitter and its contribution to homeostasis of the adult rodent hippocampus. This chapter reflects the most significant findings on cellular and molecular mechanisms from neuroscientists in the field over the last two decades. We illustrate the action of serotonin by highlighting basic receptor targeting studies, and how receptors impact brain function. We give an overview of recent genetically modified mouse models that differ in serotonin availability and focus on the role of the monoamine in antidepressant response. We conclude with a synthesis of the most recent data surrounding the role of serotonin in activity and hippocampal neurogenesis. This synopsis sheds light on the mechanisms and potential therapeutic model by which serotonin plays a critical role in the maintenance of mood.

Contents

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1. Introduction

Our knowledge of the biology of serotonin (5-hydroxytryptamine, 5-HT) and its function in the peripheral and CNS has been rapidly growing. This is likely due to the cloning of the multiple receptor subtypes that mediate serotonin signaling and the advent of new technologies to selectively perform gain- or loss-of-function studies. In this review we focus on serotonin activity in the rodent brain, and particularly concentrate on the role of serotonin in adult hippocampal neurogenesis. The discovery of newly generated neurons throughout life [2,39] has not only altered the perception of the general public that the brain lacks the capacity for neuron replacement but also opens novel fields of neuroscience research. Serotonin contributes to this fascination as one of the crucial signals in the neurogenic niche microenvironment together with other growth factors, hormones, or neurotransmitters that regulate cell proliferation and differentiation.

Neurogenic niches are only a few spatially restricted regions consisting of neural stem cells that retain fate plasticity and can respond to environmental stimuli [43,86,22]. These are the subventricular zone (SVZ), where new neurons contribute to encoding olfactory information, and the subgranular zone (SGZ) of the dentate gyrus (DG). In the adult DG, neurogenesis comprises six developmental steps, where radial glia-like stem cells (type-1, 1st) give rise to proliferating amplified progenitor cells (type-2a/b and type-3, 2nd to 4th) that become immature (5th) and mature (6th) neurons [41,35] (Fig. 1A). The common method to examine neurogenesis includes proliferation and differentiation of precursor cells that can be detected by incorporation of the thymidine analog bromodeoxyuridine (BrdU), and specific marker expression such as Sox2 (type-1 and type-2) or DCX (doublecortin) that characterizes transiently amplified progenitor cells of the neuronal lineage (type-2b/3). While proliferation is determined two to 24 h after, survival of newborn neurons is analyzed several times post-injection of BrdU; the time newborn cells get structurally and functionally integrated into the network is within three to seven weeks [52]. The young adult rat DG generates approximately 9000 cells/day (6% of the total granule cell population per month) that drastically declines with aging ([49,13]).

Serotonin plays a role in many homeostatic systems as evidenced by the results showing that deregulation of the serotonin system leads to neurogenic decline, changes in appetite, and mood disorders. Whether neurogenic decline is causative or associative with these pathologies remains to be determined. In the case of depression, chronic manipulation of serotonin by agents that inhibit serotonin reuptake, leads to clinical improvement associated with a slow, temporal increase in adult hippocampal neurogenesis [57,79]. While the mechanism of serotonin action in the hippocampus is just being illuminated, there is considerably less known regarding its function in SVZ neurogenesis [4,68].

The first part of this chapter will summarize studies on robust pharmacological depletion or enhancement of serotonin levels that affect granule cells in the DG. We will discuss the modulator role of several 5-HT receptors and their contribution to homeostasis of adult neurogenesis. As we will see, serotonin exerts a pro-neurogenic effect that is mediated through a complex network of receptors, many of which remain to be tested. We focus on the receptors addressed the most: 5-HT1A, 5-HT2A and 2C, and summarize the key findings. The review will continue with a variety of recently generated animal models that provide controlled regulation of serotonin supply and have been used to characterize alterations in baseline proliferation and survival of newborn cells. It is important to define serotonin's essential roles in brain function and behavior, as it is equally important to discover the regulators and interactive pathways by which serotonin mediates brain function. In this regard, we have recently tested serotonin action in a loss-of-function model in which the availability of brain-derived serotonin is selectively depleted [1,45]. These data together with others from genetically modified mouse models shed a distinct light on the mechanisms proposed in earlier studies to be reviewed here. We will also consider the anticipated role of serotonin in the antidepressant response and increased neurogenesis and thus address and review the monoamine/neurotrophin hypothesis. Finally we will point toward new directions for future research and discuss the promise of uncovering mechanisms where serotonin may be manipulated to affect memory and mood disorders.

1.1. The effect of pharmacological serotonin depletion or enhancement on baseline neurogenesis

Serotonin is synthesized in neurons of the brain stem raphe nuclei (reviewed in [29]) from the amino acid tryptophan by a short metabolic pathway, consisting of the neuron-specific enzyme tryptophan hydroxylase (TPH) 2 [87]. Once serotonin is synthesized it is packed into synaptic vesicles by the vesicular monoamine transporter (VMAT) 2. Extracellular levels of serotonin are regulated by its re-uptake into the presynaptic cell through its specific (serotonin) transporter (SERT). The transcription factors Lmx1b and Pet1 are expressed in serotonergic neurons in the raphe nuclei during development. Pet1 directly controls the expression of the genes encoding TPH2, 5-HT1A receptor, and SERT [53] by binding a conserved *cis*-regulatory element in these genes [33].

Serotonergic fibers project throughout the brain and into the DG of the hippocampus where they synapse with granule cells and interneurons. Here, serotonin is an important intrinsic soluble factor that promotes neuronal development [12,72,79,4]; but data on whether this stimulation primarily affects cell proliferation or survival of newly generated neurons are contradictory. First evidence of serotonin's modulator role in the adult DG originates from pharmacological manipulation studies based on lesion of serotonergic neurons in the raphe (by injection of 5,7-Dihydroxytryptamine, DHT) [12,38] or inhibition of serotonin synthesis (by para-chlorophenylalanine, PCPA) [37,38]. While the first method robustly destroys fibers and possibly cells, PCPA treatment inhibits the synthesizing enzyme TPH. Yet, both methods have been shown to decrease hippocampal serotonin levels and adult neurogenesis [12,38]. In turn, raphe grafts can restore serotonergic control and the number of proliferating precursor cells and immature neurons in the DG [12]. Serotonin depletion also leads to a decrease in dendritic spine density of granule cells [90]. However, controversial data exist showing that PCPA treatment, but not the neurotoxin 5,7-DHT [37] might decrease the number of precursor cells at 1 day and 4 weeks later [38], while chronic PCPA treatment also leads to increased survival of precursor cells in the DG of wild type animals mimicking models with serotonin deficiency [21]. On balance, data from these studies reveal that serotonin depletion or a decline in serotonin synthesis has long-term regulatory effects on adult hippocampal neurogenesis, however with noticeable contradictive effects.

Further evidence of serotonin's modulator role on generating new neurons in the adult brain has been achieved by studies on selective serotonin reuptake inhibitors (SSRIs) [56,79,25,88,44]. SSRIs mode of action is an immediate increase in the synaptic availability of serotonin with the acute administration facilitating serotonergic transmission and transient desensitization of 5-HT1A autoreceptors. Chronic treatment of this class of antidepressants induces re-establishment of the serotonin system by long-term downregulation of SERT and 5-HT1A autoreceptor activities [10,19]. Chronic, but not acute, treatment with fluoxetine (trade name 'Prozac') also leads to increased hippocampal neurogenesis,