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The role of 5-HT receptors in depression

Christine N. Yohn, Mark M. Gergues and Benjamin Adam Samuels*

Abstract: Depression is a polygenic and highly complex psychiatric disorder that remains a major burden on society. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are some of the most commonly prescribed drugs worldwide. In this review, we will discuss the evidence that links serotonin and serotonin receptors to the etiology of depression and the mechanisms underlying response to antidepressant treatment. We will then revisit the role of serotonin in three distinct hypotheses that have been proposed over the last several decades to explain the pathophysiology of depression: the monoamine, neurotrophic, and neurogenic hypotheses. Finally, we will discuss how recent studies into serotonin receptors have implicated specific neural circuitry in mediating the antidepressant response, with a focus being placed on the hippocampus.

Keywords: Serotonin, Depression, Antidepressant, Dentate gyrus, 5-HT$_{1A}$ receptor, Hippocampus, Adult neurogenesis

Introduction

Major depressive disorder (MDD) is a ubiquitous illness that plagues more than 300 million people worldwide across all races and socioeconomic groups [1, 2]. MDD often strikes early in life and remains a chronic or recurring lifelong illness, and is therefore responsible for more years lost to disability than any other illness [1]. Since MDD is characterized by diverse etiologies and an overlapping symptomology with highly comorbid disorders (i.e. anxiety), understanding the neurobiological basis of MDD is currently a major challenge for modern psychiatry and neurobiology [3, 4]. Overall, the underlying pathology of depression is extremely heterogenous and complex, which hinders the development of treatments that are effective for all depressed individuals.

Historically treatments have ranged from psychoanalysis and electroconvulsive therapy to modern medications such as antidepressants. The earliest drugs found to successfully treat depression were monoamine oxidase inhibitors (MAOIs). Iproniazid, the first MAOI, was actually developed to treat tuberculosis, but in the early 1950s it was found to elevate mood and stimulate patient activity [5]. MAOIs inhibit the oxidation of monoamines and ultimately result in increased extracellular levels of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) throughout the brain. Tricyclics (TCAs), developed in the 1950s, were also found to be moderately effective

antidepressants that increased monoamine levels mainly by blocking 5-HT and NE reuptake [6–8]. However, the acceptance and usage of these drugs were hindered by both pervasive public stigma and potentially severe side effects. By the late 1980s, second-generation antidepressants that were more pharmacologically specific, such as selective serotonin reuptake inhibitors (SSRIs), were developed and found to have improved side effect profiles. SSRIs inhibit 5-HT reuptake into raphe nuclei neurons, and chronic treatment results in increased 5-HT levels throughout the brain [9, 10]. The development of SSRIs resulted in adult use of antidepressants tripling between 1988 and 1994 and increasing an additional 48% from 1995 to 2002 [11]. Although developed several decades ago, SSRIs currently remain some of the most prescribed drugs in the world today.

The efficacy and actions of both first- and second-generation antidepressants are the principal basis of the monoamine hypothesis, which suggests that an imbalance in 5-HT, NE, and/or DA neurotransmission underlie the pathophysiology of depression [12, 13]. This hypothesis may also be supported by clinical observations dating back to the 1950s that reserpine, which depletes central stores of monoamines, can induce depression in a subset of patients [14, 15]. As for 5-HT specifically, acute tryptophan depletion induces the recurrence of mild depression symptoms in patients that demonstrated remission with 5-HT antidepressants [16–18]. Furthermore, cerebrospinal fluid levels of the primary metabolite of 5-HT (5-HIAA) appear to be lower in a subset of patients with MDD, especially those exhibiting suicidal behavior [19–21].

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However, approximately 33% of MDD patients do not respond to treatment with a commonly used SSRI and 67% of patients do not remit to this first line treatment [22, 23]. Underscoring the diverse etiologies of MDD, in recent years some research has shifted focus to potential new therapies such as noncompetitive NMDA receptor antagonists [24, 25], anticholinergic agents [26], and opioid modulators [27–29]. Therefore, it will ultimately be critical to stratify patients into distinct subsets so that they can be treated with the most appropriate and effective medications.

This review addresses the roles that both different gene polymorphisms involved in 5-HT signaling and the different 5-HT receptors (i.e. 5-HT_{1A}, 5-HT_{1B}, 5-HT_4, and 5-HT_7) may have in the pathophysiology of depression and the antidepressant response. A streamlined knowledge of these 5-HT signaling-related polymorphisms and receptors may ultimately prove instructive in determining which patients will be responsive to SSRIs. Furthermore, the determination of specific spatial populations of 5-HT receptors involved in mediating the beneficial effects of antidepressant treatment will yield a window into the neural circuitry that modulates mood-related behaviors. Therefore, we will also discuss the location of the 5-HT receptors that mediate the antidepressant response and the neural circuitry that is directly affected by altered levels of 5-HT.

SERT polymorphism

Within humans, variants that affect serotonergic function can affect disease susceptibility and response to antidepressant treatment. The most prominently studied polymorphism occurs in the promoter of the gene encoding the Serotonin Transporter (SERT), the protein that is the main target for many currently prescribed antidepressants. The promoter contains a polymorphism that results in a short (14 repeats) or long (16 repeats) allele. Individuals homozygous for the short SERT allele have decreased levels of SERT and enhanced susceptibility to stressful events and depression relative to individuals homozygous for the long SERT allele [30]. Additionally, aside from depression, the SERT polymorphism was originally proposed to account for 7–9% of the inherited variance in anxiety-related disorders [31]. However, recent genome-wide association data has found poor replication of candidate genes for MDD, including the SERT polymorphism [32]. In preclinical work, SERT deficiency is associated with increased anxiety and negative valence related behaviors in adulthood and a complete lack of responsiveness to SSRIs [33, 34].

Serotonin receptors
5-HT_{1A}
Accumulating evidence indicates a role for at least 5 of the 14 5-HT receptor subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_4,

5-HT_6, and 5-HT_7. 5-HT_{1A} receptors (5-HT_{1A}Rs) exist in two distinct populations: 1) as somatodendritic autoreceptors on the raphe nuclei neurons that produce 5-HT, and 2) as postsynaptic heteroreceptors that mediate local neuromodulatory effects in several brain areas innervated by serotonergic projections [35–38]. 5-HT_{1A}Rs are Gi/o-coupled metabotropic receptors that, when activated, suppress cyclic adenosine monophosphate (cAMP) levels and ultimately inhibit neuronal activity [39]. Activation of 5-HT_{1A} autoreceptors decreases the firing rate of raphe nuclei neurons resulting in limited 5-HT release through a negative feedback mechanism [40]. 5HT_{1A} autoreceptors are associated with the etiology of anxiety behavior, as mouse studies suggest that specific modulation of 5-HT_{1A} autoreceptor levels on raphe nuclei neurons during discrete developmental windows can alter anxiety behavior in adulthood [38, 41–43].

In addition to SERT, a polymorphism also exists in the promoter region of the gene encoding the 5-HT_{1A}R [44, 45]. This single nucleotide C(−1019) G polymorphism in the 5-HT_{1A}R promoter alters binding of the transcriptional repressors NUDR/DEAF-1 and Hes5 such that repression is greatly reduced with the G(−1019) allele [46]. Presumably the lack of repression results in increased 5-HT_{1A}R expression in the raphe nuclei of persons homozygous for the G(−1019 allele) and subsequently decreased serotonergic neuron firing. Indeed, preclinical work finds that mice deficient for the transcriptional repressor NUDR/DEAF-1 have upregulation of 5-HT_{1A} autoreceptors specifically in the raphe nuclei [47]. In humans, the G/G genotype is related to an increased risk of anxiety and MDD as well as a reduction in response to SSRI treatment [45, 48, 49].

With chronic SSRI treatment, the negative feedback mechanism that limits 5-HT release ultimately inactivates due to desensitization of the raphe 5-HT_{1A} autoreceptors and subsequent alterations in the firing rates of the serotonergic neurons, but this process can take weeks [40, 50, 51]. Through generation of transgenic mice, a preclinical study found that specifically altering levels of raphe 5-HT_{1A} autoreceptors could lead to the development of antidepressant responders and non-responders. Mice exhibiting lower levels of 5-HT_{1A} autoreceptors were more resilient to stress and more responsive to SSRI treatment than mice containing high levels of 5-HT_{1A} autoreceptors [38]. Importantly, the mice with the lower levels of 5-HT_{1A} autoreceptors also demonstrated a sub-chronic response to SSRIs in novelty suppressed feeding (NSF), a behavioral paradigm that usually requires chronic treatment of at least 14 days before an antidepressant response can be observed [38, 52]. Thus, raphe 5-HT_{1A} autoreceptors actually temporarily limit or inhibit the behavioral SSRI response due to their negative feedback on 5-HT release.

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In addition to acting as an autoreceptor, 5-HT$_{1A}$ is also a postsynaptic heteroreceptor that mediates responses to released 5-HT in several areas of the brain including the septum, hippocampus, amygdala, thalamus, and hypothalamus [53–55]. Several lines of evidence indicate a critical role for 5-HT$_{1A}$ heteroreceptors in mediating the behavioral response to antidepressant treatment. Mice that are germline deficient (lacking both 5-HT$_{1A}$ autoreceptors and heteroreceptors) do not respond to SSRIs in the NSF test, hinting at a potential role for the 5-HT$_{1A}$ heteroreceptors in mediating the behavioral response to antidepressants [56]. Additionally, chronic systemic treatment with the 5-HT$_{1A}$R agonist 8-OH-DPAT mimics the behavioral effects of antidepressant treatment in the NSF test in wild-type but not 5-HT$_{1A}$ receptor-deficient mice [56].

Chronic antidepressant treatment also results in increased adult hippocampal neurogenesis (discussed at length below), and this increase is necessary for the behavioral effects of antidepressants [56, 57]. Correlating with the behavioral effects, mice that are germline deficient for 5-HT$_{1A}$ receptors do not show an increase in adult hippocampal neurogenesis with chronic SSRI treatment [56]. Furthermore, chronic treatment with the 5-HT$_{1A}$R agonist 8-OH-DPAT also mimics the effects of antidepressants by increasing adult hippocampal neurogenesis [56].

In a recent study, Samuels and colleagues (2015) found that specific deletion of 5-HT$_{1A}$ heteroreceptors from mature granule cells (GC) in the dentate gyrus (DG), a subfield of the hippocampus, abolished the effects of SSRIs in a variety of behavioral tasks (including NSF) and attenuated the effects of SSRIs on adult neurogenesis and hippocampal neurotrophic factor expression (BDNF and VEGF) [54]. By contrast, if 5-HT$_{1A}$Rs were deleted from the young adult born granule cells (abGCs) in the DG, then the effects of SSRIs on behavior and neurogenesis remained intact. Furthermore, expressing 5-HT$_{1A}$Rs in DG GCs on a 5-HT$_{1A}$ deficient background demonstrated that this population of 5-HT$_{1A}$Rs is sufficient to mediate the behavioral and neurogenic effects of SSRIs. Overall, the results from the series of experiments conducted by Samuels and colleagues (2015) indicate that dentate gyrus 5-HT$_{1A}$ heteroreceptors on mature granule cells are a potential target for clinical therapeutics [54].

Previous clinical trials with drugs that target 5-HT$_{1A}$Rs, such as pindolol, have yielded disappointing results likely because these drugs targeted both the autoreceptor and heteroreceptor populations, which can have somewhat opposing effects [58]. Future attempts at targeting 5-HT$_{1A}$Rs should focus on specifically modulating the activity of either autoreceptors or heteroreceptors (but not both) in order to yield faster acting and/or improved antidepressants. To this end, recent pharmacological studies have reported a new generation of agonists that preferentially target 5-HT$_{1A}$R subpopulations [53, 59].

5-HT$_{1B}$

Levels of 5-HT$_{1B}$Rs are also a key determinant of stress reactivity, and therefore 5-HT$_{1B}$Rs may be a potential pharmacological target for antidepressant development [60, 61]. Unlike somatodendritic 5-HT$_{1A}$ autoreceptors, 5-HT$_{1B}$ G$_{\alpha i}$-coupled autoreceptors are located on both serotonergic and non-serotonergic presynaptic terminals throughout the brain where they inhibit neurotransmitter release [39, 50, 62–66]. Following the administration of SSRIs, mice lacking 5-HT$_{1B}$ autoreceptors exhibit increases in 5-HT levels in the ventral hippocampus (vHPC) and decreases in anxiety-like behaviors [66]. Furthermore, chronic antidepressant treatment increases 5-HT release through decreasing the expression and efficacy of the 5-HT$_{1B}$Rs in the dorsal raphe nuclei (DRN) [66–68]. However, data regarding whether 5-HT$_{1B}$Rs facilitate the antidepressant response remain somewhat contradictory as some labs have found augmenting antidepressant effects of 5-HT$_{1B}$Rs antagonists, while others have not [69–72]. Similar to the case with 5-HT$_{1A}$Rs, the inconsistent pharmacological findings may be attributed to the dual function of 5-HT$_{1B}$Rs as both heteroreceptors and autoreceptors. Additionally, due to the diffuse location of 5-HT$_{1B}$ autoreceptors that overlap with 5-HT$_{1B}$ heteroreceptors throughout the brain, it is difficult to delineate between the two distinct populations [63, 65, 66]. Similar to 5-HT$_{1A}$ heteroreceptors, 5-HT$_{1B}$ heteroreceptors on DG GCs may play a role in the SSRI-mediated increase in adult hippocampal neurogenesis [73, 74].

5-HT$_{2C}$

5-HT$_{2C}$Rs are G$_{\alpha q}$-coupled heteroreceptors that are expressed in several limbic structures including the hippocampus (especially enriched in CA3), amygdala, anterior olfactory and endopiriform nuclei, and cingulate and piriform cortex. Overactivity of 5-HT2CRs may contribute to the etiology of depression and anxiety as some suicide victims have abnormally high expression of 5-HT$_{2C}$Rs in the prefrontal cortex [75]. Agomelatine, a mixed melatonergic agonist/5-HT$_{2C}$R antagonist is an effective anxiolytic and antidepressant in both preclinical and clinical populations [76–80]. Furthermore, acute administration of SSRIs can lead to negative side effects (such as increased anxiety) presumably through activation of both 5-HT$_{1A}$R autoreceptors and 5-HT$_{2C}$R heteroreceptors [81–85].

Interestingly, a recent study from Marcinkiewcz et al. showed that 5-HT release from the dorsal raphe nucleus enhances fear and anxiety through activation of 5-HT$_{2C}$Rs on a subpopulation of corticotropin-releasing factor (CRF) neurons in the bed nucleus of the stria terminalis (BNST) [86]. Ultimately, activation of these CRF neurons in the

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BNST engages an inhibitory microcircuit that silences outputs to the ventral tegmental area and lateral hypothalamus. Furthermore, Marcinkiewcz et al. demonstrated that acute SSRI treatment potentiates anxiety-like behavior and that this effect was blocked by specific chemogenetic inhibition of CRF neurons in the BNST [86]. Taken together, these results suggest that 5-HT$_{2C}$Rs in the BNST underlie the negative effects of acute SSRI administration.

5-HT$_4$

5-HT$_4$Rs are G$_{\alpha s}$-coupled receptors that increase intracellular cAMP levels via adenylyl cyclase function to increase neuronal activity [39]. 5-HT$_4$ heteroreceptors are widely expressed in limbic regions, including the amygdala, septum, and hippocampus as well as the mesolimbic system [39, 55].

The C-terminal tail of the 5-HT$_4$R is subject to complex diversity due to alternative splicing of the mRNA resulting in several different variants [39]. Within this splice variant region are polymorphisms that are associated with susceptibility to unipolar depression [87]. In addition, a postmortem study revealed alterations in both 5-HT$_4$R binding and cAMP concentration levels in several brain regions of depressed violent suicide victims [88]. One report also suggests that lower striatal 5-HT$_4$R binding in humans may contribute to the etiology of MDD [89]. Together these results implicate a role for 5-HT$_4$Rs in mood disorders.

5-HT$_4$R expression is also associated with the development of some behavioral features of depression, since the deletion of or pharmacological blockade of 5-HT$_4$Rs results in increased depressive and anxiety-like behaviors in rodents [74, 90, 91]. Interestingly, the 5-HT$_4$R agonist (RS67333) produces rapid antidepressant effects after only three days of administration in rodents [92]. This short treatment window appears to be enough to both desensitize 5-HT$_{1A}$ autoreceptors and increase hippocampal neurogenesis. A more recent study comparing RS67333 to fluoxetine (FLX) found that RS67333 induced anxiolytic-like effects in several behavioral tests after only 7 days, confirming that 5-HT$_4$R agonists provide more rapid effects than currently used antidepressants [93]. Interestingly, administration of a 5-HT$_4$R antagonists do not block the behavioral effects of SSRIs, indicating that 5-HT$_4$R activation likely mediates anxiolytic-like effects via a distinct mechanism [94]. Thus, more research is needed to determine the therapeutic potential of 5-HT$_4$Rs as a target for treating anxiety and depression.

5-HT$_6$

5-HT$_6$Rs are postsynaptic G$_{\alpha s}$-coupled heteroreceptors that are enriched in the striatum, nucleus accumbens (NAc), and cortex, with moderate expression in the

hippocampus, amygdala, and hypothalamus [39]. A recent study found that two distinct agonists that are selective for 5-HT$_6$Rs both produce antidepressant and anxiolytic-like effects in rodents [95]. Somewhat paradoxically, 5-HT$_6$R antagonists also can induce antidepressant- and anxiolytic-like effects in rodent models [96–99]. It is currently unclear whether these similar behavioral outcomes are due to diverse neurochemical effects associated with 5-HT$_6$R agonists and antagonists or whether distinct actions are being mediated in different brain regions [74, 98]. Future studies are necessary to further explore the role of 5-HT$_6$R receptor subtypes in antidepressant-like responses.

5-HT$_7$

5-HT$_7$ are G$_{\alpha s}$-coupled heteroreceptors located in the limbic and cortical regions of the brain [39]. Hippocampal 5-HT$_7$Rs appear to be involved in the interaction between the serotonergic system and the hypothalamus-pituitary-adrenal (HPA) axis since 5-HT$_7$R agonists increase glucocorticoid receptor expression in hippocampal cell cultures [100]. Acute but not chronic, restraint stress increases 5-HT$_7$R mRNA in hippocampal subregions CA2 and CA3 [101]. Antidepressant administration downregulates 5-HT$_7$ in the hypothalamus [102]. Mice lacking 5-HT$_7$Rs exhibit antidepressant-like behaviors in stressful environments and pharmacological blockade of 5-HT$_7$Rs results in a faster antidepressant responses in rats [97, 103–107]. Furthermore, the atypical antipsychotic, amisulpride, also acts as an antidepressant that is a high affinity 5-HT$_7$R antagonist. Interestingly, the antidepressant-like behavioral effects of amisulpride are abolished in mice lacking 5-HT$_7$Rs [108]. Therefore, 5-HT$_7$Rs antagonists may also represent a new class of antidepressants that could have faster therapeutic action in treating depression.

Serotonin and Neurotrophic factors

Since the original development of the monoamine hypothesis of depression, more recent data has expanded this theory to the non-mutually exclusive neurotrophic and neurogenesis hypotheses. These hypotheses speculate that decreases in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) or decreases in adult hippocampal neurogenesis are respectively involved in the pathophysiology of depression, and that their restoration is critical for the therapeutic efficacy of antidepressant treatment [109–113]. 5-HT signaling and 5-HT receptors are heavily involved in regulating the levels of both neurotrophic factors and adult hippocampal neurogenesis.

The neurotrophic hypothesis is supported by the idea that stress and/or depression decrease expression of various neurotrophic factors (i.e. BDNF) in limbic areas and this decrease correlates with neuronal atrophy

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[110, 111, 114]. Specifically, following exposure to stressful experiences researchers have observed decreases in BDNF in rodent hippocampus and prefrontal cortex [109, 111, 115, 116]. Similarly, in humans, postmortem studies find reduced levels of BDNF in these regions of depressed patients [111, 117, 118]. In both humans and rodents, chronic SSRI treatment increases BDNF levels [111, 119, 120] with BDNF signaling required for adult hippocampal neurogenesis, synaptic plasticity, and neuronal remodeling [121, 122]. In mice lacking BDNF in the forebrain or the BDNF receptor Tropomysin receptor kinase B (TrkB) in adult DG neural precursor cells (NPCs), the behavioral and adult neurogenic response to SSRI treatment is eliminated [121, 123]. SSRI administration increases the maturation of young abGCs, as measured by dendritic arborization complexity [124]. BDNF and activation of its receptor TrkB have similar effects on maturation of young adult born neurons, suggesting that BDNF may mediate some of the effects of SSRIs on neurogenesis [125–128]. Interestingly, direct infusions of BDNF into the DG of rodents results in antidepressant-like behavioral effects [129].

In addition to BDNF, other neurotrophic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), insulin-like growth factor 1 (IGF1), and Activin-A are also increased by antidepressant treatment. Unlike the established association between BDNF levels and adult hippocampal neurogenesis, these neurotrophic factors are implicated to varying degrees in mediating effects on neurogenesis and synaptogenesis [127, 130–136]. Similar to BDNF, direct cerebral infusions of any one of these growth factors can result in antidepressant-like behavioral responses [127, 129, 130, 134, 136, 137].

In humans, a common single nucleotide polymorphism (SNP) that results in a methionine substitution for valine at codon 66 (Val66Met) in the 5′ pro-domain of the BDNF coding region occurs in 25–32% of the Caucasian population and in 40–50% of the Asian population [138–140]. In the Caucasian population, the Val/Val allele is associated with higher neurotic scores and higher levels of trait anxiety than subjects with the Val/Met or Met/Met genotypes. By contrast, in Asian populations, the Met/Met allele is associated with expression of suicidal and psychotic symptoms and depression in the elderly [141, 142]. Chen and colleagues (2006) recreated this SNP in mice and observed that the BDNF variant (Met/Met) mice had increased anxiety related behaviors when placed in a stressful environment [143]. Furthermore, antidepressants were ineffective in treating this increased anxiety [143].

Some recent studies suggest that there may be epistatic interactions between the C(−1019)G polymorphism in the promoter of the gene encoding 5-HT$_{1A}$R and other gene polymorphisms such as the SNP found in the gene encoding BDNF [144–146]. As an example, subjects with both the G/G genotype in the 5-HT$_{1A}$R promoter and at least one copy of the Met allele of the BDNF Val66Met polymorphism had a greater than three times higher risk of treatment resistant depression [144].

Several studies attempt to directly link the role of BDNF and other neurotrophic factors with 5-HT receptors and signaling [54, 147–149]. For instance, in vitro studies show that BDNF dose-dependently decreases 5-HT reuptake, suggesting a direct effect on the function of SERT [150]. Since expression of BDNF and other neurotrophic factors are positively regulated by activity, activation of 5-HT receptors positively coupled to cAMP levels (such as 5-HT$_4$ and 5-HT$_7$) should yield enhancement of neurotrophic factor levels. The 5-HT$_4$R agonist RS67333 increases BDNF mRNA expression in the hippocampus [151]. Furthermore, in vitro studies show that the 5-HT$_7$R agonist LP12 increases expression of the BDNF receptor TrkB [152]. By contrast, specific deletion of 5-HT$_{1A}$Rs, which are negatively coupled to cAMP levels, from mature DG GCs attenuates the chronic SSRI-induced increase in BDNF and VEGF levels [54]. While there is precedent for 5-HT$_{1A}$R mediated regulation of VEGF levels in the dentate gyrus, this data is surprising given that 5-HT$_{1A}$Rs receptors are inhibitory and both BDNF and VEGF activity are induced by activity [39, 153]. However, since findings from Samuels and colleagues (2015) are based on chronic, not acute, SSRI administration, it is possible that the effects are mediated through an indirect downstream mechanism that has yet to be resolved [54].

The FGF receptor FGFR1 can form heteroreceptor complexes with 5-HT$_{1A}$Rs in the hippocampus and raphe nucleus [131, 154, 155]. Treatment with 5-HT$_{1A}$R agonists or SSRIs results in activation of FGFR1 signaling [131, 156]. Additionally, transactivation of these receptor complexes results in synergistic increases in neurite density and protrusions, suggesting a combined role of FGFR1 and 5-HT$_{1A}$Rs in synaptogenesis [156]. Furthermore, formation of FGFR1–5-HT$_{1A}$R heterocomplexes may cause uncoupling of GIRK-5-HT$_{1A}$R heterocomplexes in the raphe nuclei [154]. Theoretically would decrease 5-HT$_{1A}$R autoreceptor function, so direct targeting of FGFR1–5-HT$_{1A}$R heterocomplexes could result in faster acting antidepressants. Overall, 5-HT receptors and neurotrophic factors appear to be synergistically involved in both the pathophysiology of depression and the antidepressant response.

Serotonin and Neurogenesis

Over the last two decades, it has become accepted that new neurons are produced in mammals in two discrete locations, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the DG in the hippocampus [157]. The neurons born in the SVZ

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migrate through the rostral migratory stream into the olfactory bulb and become interneurons, while those born in the SGZ migrate into the granular layer of the DG and eventually develop into mature granule neurons. The process of adult neurogenesis involves several steps, which include proliferation and fate specification of neural progenitors, neuronal migration and maturation, as well as synaptic integration of young neurons into the existing neuronal circuitry. Various well-established molecular markers are used to identify cells at distinct points, with electrophysiological cell membrane properties well understood throughout the neurogenesis process [157, 158].

Chronic, but not acute, antidepressant treatment increases proliferation of dividing NPCs in the SGZ, differentiation of precursor cells into young abGCs, and the rate by which young abGCs mature and integrate into the DG circuitry [57, 124]. Furthermore, the effects of chronic antidepressants seem to be specific to the SGZ as they do not increase neurogenesis in the SVZ [57, 159]. Critically, ablation of the adult hippocampal neurogenic niche, by focal radiological approaches, results in a loss of the behavioral antidepressant response, suggesting a necessary role for adult neurogenesis in mediating the behavioral effects of chronic antidepressant treatment [56, 160, 161]. These studies directly resulted in the neurogenesis hypothesis [112, 113]. However, it is important to note that ablation of adult hippocampal neurogenesis in rodents does not result in increases in anxiety- and depression-related behaviors [56, 161]. Similarly, while decreases in the number of DG GCs have been found in postmortem samples of untreated depressed patients, there does not appear to be a decrease in the number of progenitor cells [162]. Furthermore, specifically enhancing neurogenesis via a genetic approach does not result in an antidepressant-like phenotype under baseline conditions [163]. Therefore, while increasing adult hippocampal neurogenesis is necessary for the antidepressant response, it is not sufficient to mediate an antidepressant response and there is limited data to suggest that decreases in adult hippocampal neurogenesis may underlie the pathophysiology of depression.
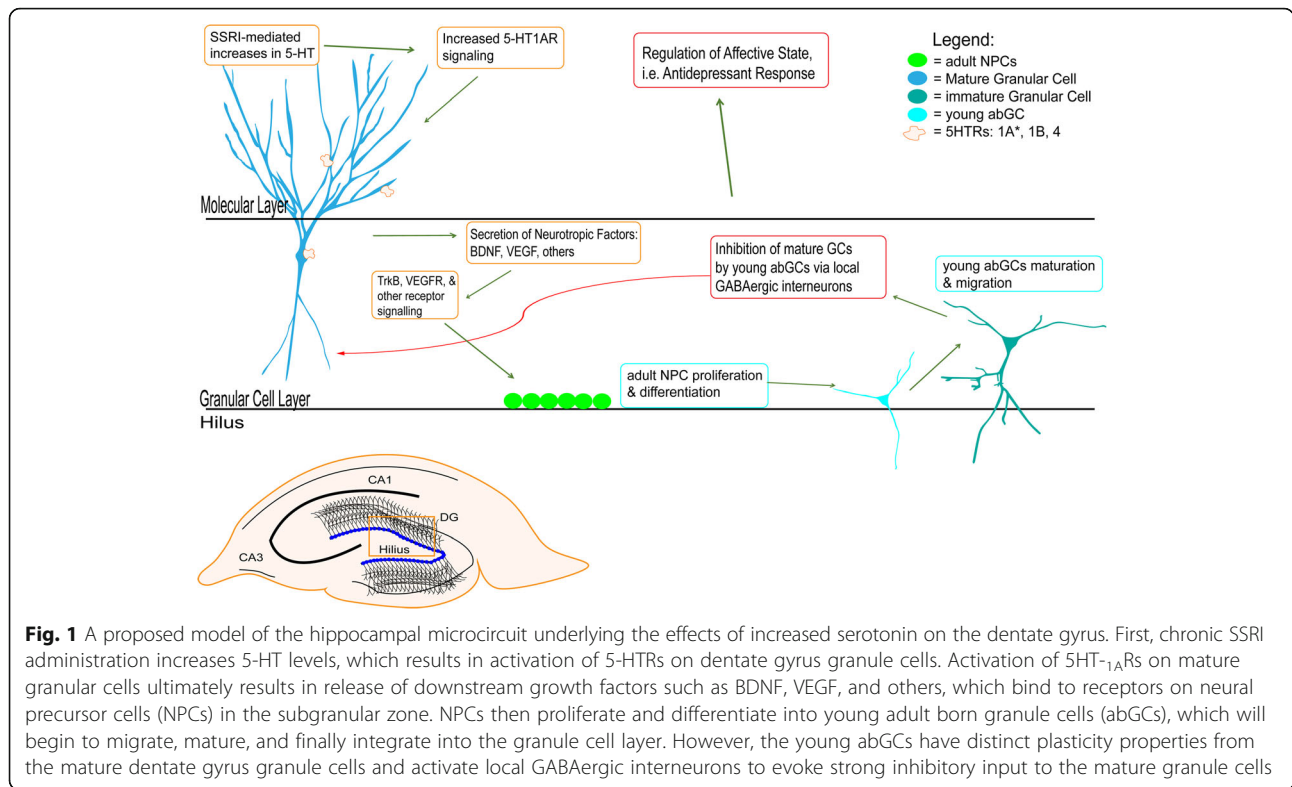
The mechanisms by which SSRIs increase adult hippocampal neurogenesis is likely mediated by several different 5-HT receptors. Administration of the $5HT_{1A}R/5-HT_7R$ agonist 8-OH-DPAT increases neurogenesis in both the SGZ and SVZ [56, 73]. Furthermore, SSRIs do not increase neurogenesis in mice that are germline deficient for $5-HT_{1A}Rs$ [56]. Interestingly, the recent study by Samuels and colleagues demonstrated that specific deletion of $5-HT_{1A}Rs$ from mature DG GCs, but not from young abGCs, abolished the behavioral response to SSRI treatment and attenuated the neurogenic response [54]. Taken together, these data indicate that $5-HT_{1A}Rs$ are likely a major target for SSRI-induced increases in adult hippocampal neurogenesis.

Similar to $5HT_{1A}Rs$, $5-HT_4Rs$ appear to be associated with adult neurogenesis, since $5-HT_4R$ agonists increase neurogenesis in the DG and in the enteric nervous system [92, 93, 151, 164–166]. By contrast, $5-HT_4R$ antagonists reduce differentiation of NPCs with minimal effect on cell proliferation, maturation, or morphology [93, 164]. Furthermore, the beneficial effects of $5-HT_4R$ agonists are not only rapid acting on behavior but also on adult hippocampal neurogenesis. Three days of treatment with the $5-HT_4R$ agonist RS67333 significantly increases adult hippocampal neurogenesis [92, 151]. However, recent data suggests that the rapid behavioral effects of $5-HT_4R$ agonists are mediated by a neurogenesis-independent mechanism [93]. Importantly, similar to $5-HT_{1A}R$, mice that are $5-HT_4R$ germline deficient also show an attenuated neurogenic response to chronic SSRI treatment [167].

One interesting alternative to the traditional neurogenesis hypothesis is that SSRI treatment may also cause mature GCs in the DG to undergo a dematuration process that yields cells with properties more similar to young abGCs. Chronic SSRI treatment causes a decrease in expression of the mature granule cell marker calbindin in the DG [167, 168]. Therefore, it is possible that what is commonly measured to be maturation of young adult born granule cells (assessed by dendritic complexity of Dcx-positive cells) could also be dematuration of previously mature granule cells. Furthermore, this dematuration phenomenon is attenuated in mice germline deficient for the $5-HT_4R$ [168]. Further studies have found that chronic SSRI treatment can also induce dematuration of parvalbumin-positive interneurons in the basolateral amygdala and the frontal cortex in adult mice [169, 170]. Thus, the antidepressant response may rely on both increases in neurogenesis and dematuration. It would be particularly interesting to determine whether signaling via distinct serotonin receptors can result in either increases in neurogenesis or dematuration. Further work using both spatially restricted $5-HT_{1A}R$ and $5-HT_4R$ deficient mice is required to further address this hypothesis.
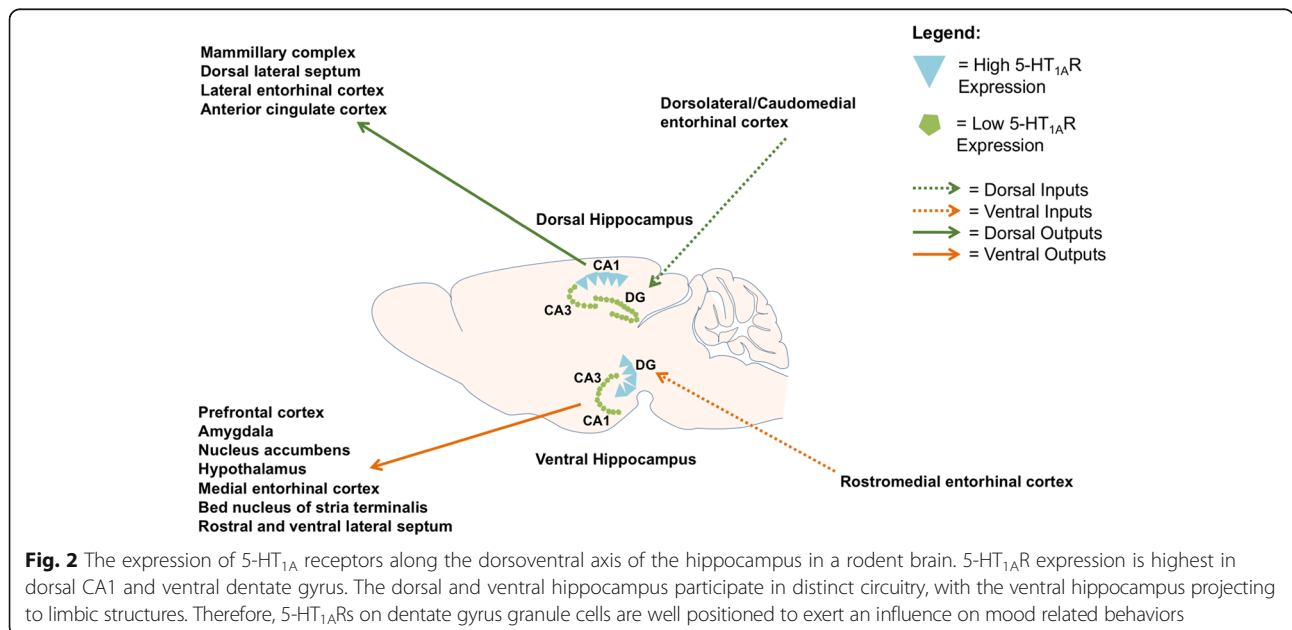
In addition, while not nearly as well established as SGZ and SVZ adult neurogenesis, several studies have suggested that adult neurogenesis can occur in other brain regions such as the cortex and hypothalamus [171–173]. A recent study by Ohira and colleagues (2013) found that SSRI treatment increased cortical inhibitory neuron proliferation [173]. Some have speculated that GABAergic interneurons are involved in the etiology of depression [174], so it will be interesting to determine whether cortical neurogenesis plays a role in mediating the beneficial effects of antidepressants on behavior.

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Fig. 1 A proposed model of the hippocampal microcircuit underlying the effects of increased serotonin on the dentate gyrus. First, chronic SSRI administration increases 5-HT levels, which results in activation of 5-HTRs on dentate gyrus granule cells. Activation of 5HT-$_{1A}$Rs on mature granular cells ultimately results in release of downstream growth factors such as BDNF, VEGF, and others, which bind to receptors on neural precursor cells (NPCs) in the subgranular zone. NPCs then proliferate and differentiate into young adult born granule cells (abGCs), which will begin to migrate, mature, and finally integrate into the granule cell layer. However, the young abGCs have distinct plasticity properties from the mature dentate gyrus granule cells and activate local GABAergic interneurons to evoke strong inhibitory input to the mature granule cells

Serotonin and the neural Circuity of the hippocampus

The results from Samuels and colleagues (2015) suggest that 5-HT$_{1A}$Rs on mature DG GCs are critical mediators of the effects of SSRIs on behavior, neurotrophic factors, and neurogenesis [54]. We propose that chronic activation of 5-HT$_{1A}$Rs on mature DG GCs activate signaling cascades that ultimately result in secretion of neurotrophic factors, such as BDNF and VEGF, which in turn stimulate proliferation of NPCs as well as differentiation and maturation of young abGCs (Fig. 1). The young abGCs, which have distinct plasticity properties from the mature DG GCs, can then activate local GABAergic interneurons to evoke strong inhibitory input to the

Fig. 2 The expression of 5-HT$_{1A}$ receptors along the dorsoventral axis of the hippocampus in a rodent brain. 5-HT$_{1A}$R expression is highest in dorsal CA1 and ventral dentate gyrus. The dorsal and ventral hippocampus participate in distinct circuitry, with the ventral hippocampus projecting to limbic structures. Therefore, 5-HT$_{1A}$Rs on dentate gyrus granule cells are well positioned to exert an influence on mood related behaviors

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mature GCs [175–178] (Fig. 1). In this model inhibition of mature GCs via direct activation of 5-HT$_{1A}$Rs or via the local microcircuitry is therefore critical for the antidepressant response.

Interestingly, 5-HT$_{1A}$Rs show a unique expression pattern in the rodent DG as expression levels dramatically increase along the dorsoventral axis to the point that the vast majority of DG 5-HT$_{1A}$Rs are expressed in the ventral pole [55]. Several studies imply that the dorsal hippocampus (dHPC) and vHPC may serve different functions, where the dHPC is more involved in cognitive functions, while the vHPC is important in regulating emotional affective states [179]. For instance, dHPC lesions reduce spatial memory in Morris water maze and radial arm maze whereas by vHPC lesions do not impair spatial memory [180, 181]. More modern approaches demonstrate that specific optical stimulation (via channel rhodopsin 2, ChR2) of basolateral amygdala (BLA) to vHPC projections or vHPC projections to NAc increases anxiety-related behaviors [182, 183]. By contrast, inhibition of vHPC projections to medial prefrontal cortex (mPFC) decreases anxiety-related behavior [184]. Directly activating granule neurons in the dorsal DG with acute stimulation of ChR2 reduces freezing behavior and recall in the contextual fear conditioning paradigm, however, this effect is not seen when stimulating the vHPC [181]. Furthermore, acute optogenetic inhibition (using halorhodopsin) of dorsal DG, but not ventral DG, leads to reductions in freezing behavior when photoillumination occurs during encoding and mice are tested 24 h later. By contrast, acute optogenetic inhibition of ventral DG but not dorsal DG results in anxiolytic-like behavioral effects.

The different roles dorsal and ventral DG have in mediating diverse behaviors is likely due to a distinct connectivity. Dorsal DG receives inputs from dorsolateral and caudomedial entorhinal cortex, and medial septal nucleus, which relay inputs from V1, S1, and thalamic nuclei. Efferent outputs from dorsal DG are sent to the mammillary complex, dorsal lateral septum, lateral entorhinal cortex, and anterior cingulate cortex [179, 185] (Fig. 2). Many of these regions are critical for memory, locomotion, and exploration, thereby demonstrating the importance of the dHPC in cognitive rather than mood related tasks. Conversely, the ventral DG receives inputs from rostromedial entorhinal cortex and medial septal nucleus that convey information from auditory and piriform cortices. Unlike dorsal DG, ventral DG projects to areas important for regulating emotional affect, with outputs extending to the prefrontal cortex, NAc, hypothalamus, amygdala, medial entorhinal cortex, BNST, as well as rostral and ventral lateral septal nuclei (Fig. 2) [179, 185].

Aside from circuit connectivity, there are electrophysiological, molecular, and anatomic differences between the dHPC and vHPC [179]. The vHPC has higher levels of 5-HT and 5-HT innervation relative to the dHPC, demonstrating the importance of 5-HTR signaling within the vHPC in potentially mediating emotional affect and antidepressant response [186]. In the hippocampus, 5-HT$_{1A}$Rs are highly expressed in the ventral DG and dorsal CA1, two distinct hippocampal subfields [55] (Fig. 2). Given that dentate gyrus 5-HT$_{1A}$Rs are necessary and sufficient for mediating the behavioral effects of SSRIs, their location in the ventral pole positions these receptors to directly influence limbic circuitry in order to regulate mood-related behavior. Future work is necessary to determine whether specific pharmacological or electrical manipulations of ventral DG may be a novel therapeutic avenue for the treatment of depression and anxiety.

Abbreviations
5-HT: Serotonin; 5-HT$_{1A}$: Serotonin receptor 1A; 5-HT$_{1B}$: Serotonin receptor 1B; 5-HT$_{2C}$: Serotonin receptor 2C; 5-HT$_4$: Serotonin receptor 4; 5-HT$_6$: Serotonin receptor 6; 5-HT$_7$: Serotonin receptor 7; abGCs: Adult born granule cells; BDNF: Brain-derived neurotrophic factor; cAMP: Cyclic adenosine monophosphate; ChR2: Channelrhodopsin 2; DA: Dopamine; DG: Dentate gyrus; DHPC: Dorsal hippocampus; DRN: Dorsal raphe nucleus; GC: Granule cells; GCL: Granular cell layer; HPA: Hypothalamic-pituitary-adrenal; IGF: Insulin-like growth factor; MAOIs: Monoamine oxidase inhibitors; MDD: Major Depressive Disorder; NE: Norepinephrine; NPC: Neural progenitor cells; NSF: Novelty suppressed feeding; SERT: Serotonin transporter; SGZ: Subgranular zone; SSRIs: Selective serotonin reuptake inhibitors; SVZ: Subventricular zone; TCAs: Tricyclic antidepressants; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; VHPC: Ventral hippocampus

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