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Rethinking 5-HT$_{1A}$ Receptors: Emerging Modes of Inhibitory Feedback of Relevance to Emotion-Related Behavior

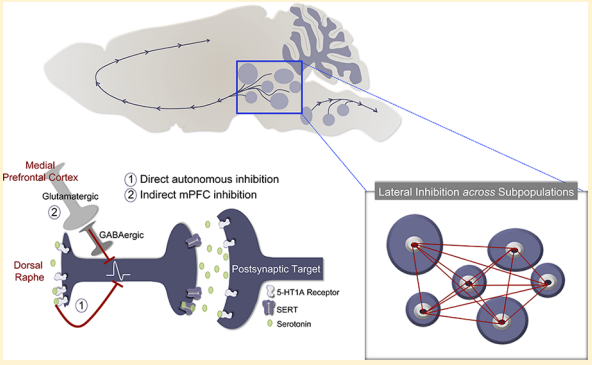
Stefanie C. Altieri,[†,⊥] Alvaro L. Garcia-Garcia,[∥,⊥] E. David Leonardo,[*,∥] and Anne M. Andrews[*,†,‡,§]

[†]Semel Institute for Neuroscience & Human Behavior, Hatos Center for Neuropharmacology, David Geffen School of Medicine, [‡]Department of Chemistry and Biochemistry, and [§]California NanoSystems Institute, University of California, Los Angeles, California 90095, United States

[∥]Department of Psychiatry, Division of Integrative Neuroscience, Columbia University and New York State Psychiatric Institute, New York, New York 10032, United States

Supporting Information

ABSTRACT: The complexities of the involvement of the serotonin transmitter system in numerous biological processes and psychiatric disorders is, to a substantial degree, attributable to the large number of serotonin receptor families and subtypes that have been identified and characterized for over four decades. Of these, the 5-HT$_{1A}$ receptor subtype, which was the first to be cloned and characterized, has received considerable attention based on its purported role in the etiology and treatment of mood and anxiety disorders. 5-HT$_{1A}$ receptors function both at presynaptic (autoreceptor) and postsynaptic (heteroreceptor) sites. Recent research has implicated distinct roles for these two populations of receptors in mediating emotion-related behavior. New concepts as to how 5-HT$_{1A}$ receptors function to control serotonergic tone throughout life were highlights of the proceedings of the 2012 Serotonin Club Meeting in Montpellier, France. Here, we review recent findings and current perspectives on functional aspects of 5-HT$_{1A}$ auto- and heteroreceptors with particular regard to their involvement in altered anxiety and mood states.



KEYWORDS: *Serotonin, autoreceptor, heteroreceptor, development, behavior, anxiety, antidepressant*

HISTORICAL PERSPECTIVE

Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine neurotransmitter and neurohormone formed by the hydroxylation and subsequent decarboxylation of the essential dietary amino acid L-tryptophan. Serotonin is found primarily in the gastrointestinal tract, platelets, blood vessels, thyroid, pancreas, mammary glands,[1−5] and central nervous system (CNS).[6,7] In the brain, serotonin is thought to be a key modulatory neurotransmitter involved in the regulation of numerous physiological and behavioral processes including mood- and anxiety-related behavior, cognitive function, food intake, sexual behavior, sleep, cardiovascular function, blood pressure, pain, body temperature, and others.[8−11]

Serotonin was first reported in 1937 by Vialli and Erspamer and named enteramine.[12,13] In 1948, it was identified as a vasoconstrictor in blood serum where it was referred to as "serotonin".[14] Afterward, scientists realized that enteramine and serotonin were one in the same.[15,16] Serotonin was recognized as a neurotransmitter when it was discovered in extracts from mammalian brain.[17,18] In 1986, the pharmacology of serotonin was reviewed,[19] and for the first time the existence of three receptor families (5-HT1−3) was described; additional families were suspected. It is now known that the effects of serotonin are mediated by at least 14 different receptors, which are grouped into subfamilies based on pharmacological responses to specific ligands, sequence similarities at the gene and amino acid levels, gene organization, and second messenger coupling pathways.[20−23] Serotonin receptors are assigned to one of seven families, 5-HT$_{1-7}$, with individual subtypes further designated by letters.

Among serotonin receptors, much attention has been focused on the 1A subtype (5-HT$_{1A}$). The human 5-HT$_{1A}$ receptor was cloned in 1987 as a single intronless gene[24] located on chromosome 5 (5q11.2-q13). In mice, the *Htr1a* gene resides on the distal part of chromosome 13. The 5-HT$_{1A}$ receptor protein consists of 422 amino acids. Evidence from human and rodent studies suggests that 5-HT$_{1A}$ receptors are implicated in a variety of physiological and pathological processes, such as learning, memory, schizophrenia, Parkinson's disease, and notably in the etiology and treatment of mood and anxiety disorders.[25−32]

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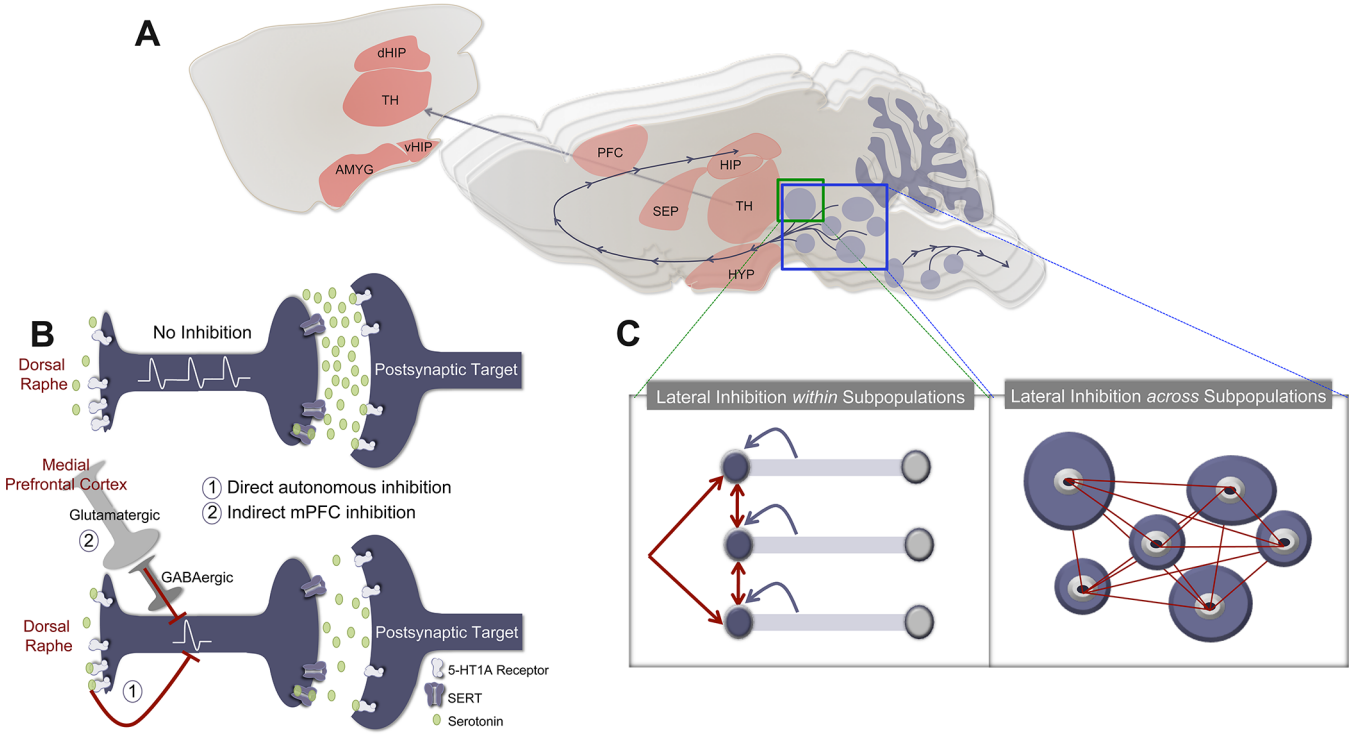

Figure 1. Inhibitory mechanisms of 5-HT$_{1A}$ autoreceptors. (A) Serotonergic cell bodies expressing 5-HT$_{1A}$ autoreceptors are located deep within the brainstem (blue box). Serotonin neurons projecting to the forebrain are organized into two main clusters designated as dorsal and median raphe nuclei with distinct subpopulations within these primary nuclei. 5-HT$_{1A}$ heteroreceptors are localized postsynaptically in various brain regions including the hippocampus (HIP), prefrontal cortex (PFC), thalamus (TH), lateral septum (SEP), amygdala (AMYG), and hypothalamic nuclei (HYP). Many of these regions have been associated with the pathophysiology of mood and anxiety disorders. (B) The top panel depicts a "conventional" serotonin synapse. In the bottom panel, activation of 5-HT$_{1A}$ autoreceptors controls serotonergic tone via one-to-one autoinhibitory feedback to reduce firing rates of serotonin neurons. 5-HT$_{1A}$ heteroreceptors also regulate serotonergic activity through descending glutamatergic projections originating in the medial prefrontal cortex (mPFC). This pathway makes connections with serotonin neurons via brainstem GABAergic inhibitory interneurons. (C) Current hypotheses regarding inhibitory mechanisms of 5-HT$_{1A}$ autoreceptor activation paint a more complex picture. For instance, emerging evidence suggests that serotonin neurons within a subpopulation or even across subpopulations affect each other via "lateral inhibition". Taken together, new perspectives on the functional aspects of 5-HT$_{1A}$ receptors associated with regulation of serotonergic activity are important avenues for future investigation, particularly regarding increased understanding of the roles of 5-HT$_{1A}$ receptors in the etiology and treatment of psychiatric disorders.

■ ADULT EXPRESSION AND FUNCTION OF 5-HT$_{1A}$ RECEPTORS

Direct Autonomous Inhibition. In the mammalian brain, 5-HT$_{1A}$ receptors are divided into two distinct classes based on localization. The cell bodies of central serotonergic neurons are found in the raphe nuclei in the brain stem (Figure 1A),[33,34] where 5-HT$_{1A}$ receptors are located on soma and dendrites.[35−37] These 5-HT$_{1A}$ autoreceptors exert inhibitory feedback in response to local release of serotonin in the raphe nuclei from axonal collaterals (Figure 1B).[38−43] Additionally, sources of local serotonin release have been proposed to arise from somatic and dendritic sites on serotonergic neurons.[44−46] Serotonin release in the cell body region results in reductions in serotonergic pacemaker activity and suppression of serotonin synthesis, turnover, and release in projection areas.[47−51] In support of this, constitutive 5-HT$_{1A}$ knockout mice show increased rates of serotonin neuronal discharge[52] and elevated basal dialysate serotonin levels in frontal cortex and hippocampus.[53]

Indirect Inhibition from Medial Prefrontal Cortex. 5-HT$_{1A}$ receptors are also expressed by nonserotonergic pyramidal, GABAergic, and cholinergic neurons[54−58] in limbic regions such as prefrontal cortex, hippocampus, lateral septum, and amygdala, as well as in several hypothalamic and thalamic nuclei (Figure 1A).[37,59,60] Activation of 5-HT$_{1A}$ heteroreceptors mediates hyperpolarizing responses to released serotonin, which typically reduces postsynaptic neuronal excitability and firing rates.[37,40,59] As such, 5-HT$_{1A}$ heteroreceptors are involved in the modulation of other neurotransmission systems. For example, 5-HT$_{1A}$ receptors in the medial prefrontal cortex (mPFC) modulate dopamine cell firing and release.[61−63]

In addition to direct/local 5-HT$_{1A}$ receptor-mediated autoregulation, evidence exists for an indirect negative feedback mechanism that involves 5-HT$_{1A}$ heteroreceptors in the mPFC (Figure 1B).[64−66] The mPFC-dorsal raphe nucleus (DRN) pathway comprises glutamatergic descending projections that are hypothesized to decrease serotonin cell firing by activating DRN GABAergic interneurons to inhibit serotonin release.[65−72] This pathway has been suggested as one of the neuroanatomical substrates controlling the effects of stress by preventing overactivation of DRN serotonergic neurons.[73] A minor glutamatergic pathway may also exist from the mPFC that excites serotonin cell firing directly in the DRN.[68,69] It is still not well understood how inhibitory 5-HT$_{1A}$ heteroreceptors excite cortical glutamatergic neurons. The most plausible explanation is the disinhibition of glutamatergic neurons via mPFC GABA interneurons expressing 5-HT$_{1A}$ heteroreceptors.[58,74] However, further studies are required to

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determine the specific mechanisms of 5-HT$_{1A}$ receptors in the mPFC.

Intracellular Signaling. 5-HT$_{1A}$ receptors are inhibitory G-protein coupled receptors (GPCRs). Early studies identified that 5-HT$_{1A}$ receptors function by coupling to Gi/Go proteins in most cells.[75] Extracellular receptor binding of serotonin or 5-HT$_{1A}$ agonists leads to intracellular exchange of GDP for GTP on Gi/Go alpha subunits. This, in turn, inhibits adenylyl cyclase, which reduces cAMP levels and protein kinase A activity.[76] Furthermore, agonist-induced activation of 5-HT1A receptors results in potassium channel activation and calcium channel inhibition.[25,59,77−80] 5-HT$_{1A}$ receptors are coupled to different GPCR pathways based on localization.[81] 5-HT$_{1A}$ autoreceptors couple exclusively to Gαi3 leading to partial inhibition of adenylyl cyclase,[82−85] an effect that may depend on specific agonists.[83,86,87] By contrast, 5-HT$_{1A}$ heteroreceptors couple mainly to Gαo in the hippocampus, and equally to Gαo and Gαi3 in cerebral cortex.[88] Differences in 5-HT$_{1A}$ Gα subunit coupling might explain regional differences in activation versus inhibition of intracellular signaling pathways. 5-HT$_{1A}$ autoreceptor desensitization is more pronounced compared to 5-HT$_{1A}$ heteroreceptor desensitization, which also could be related to differential Gα coupling.[88,89] Stimulation of 5-HT$_{1A}$ receptors also leads to activation of G-protein-coupled inward rectifying potassium channels (GIRKs)[90] in raphe neurons[86,91−95] and hippocampus.[96−98] Whether 5-HT$_{1A}$ receptors fully couple to inhibit adenylyl cyclase remains controversial, as it has been suggested that the hyperpolarizing response mediated by 5-HT$_{1A}$ autoreceptors is due to the activation of GIRK channels via G-protein $\beta\gamma$ subunits.[99]

In addition to their canonical function, 5-HT$_{1A}$ receptors activate growth factor-regulated signaling pathways, such as mitogen-activated protein kinases (MAPK) and Akt signaling pathways.[25] In MAPK signaling, ERK is preferentially affected by 5-HT$_{1A}$ receptors. For example, in RN46A cells, a model of serotonergic raphe neurons that express endogenous 5-HT$_{1A}$ receptors, adenylyl cyclase and ERK1/2 phosphorylation were inhibited by 5-HT$_{1A}$-receptor activation.[100] However, in hippocampal-derived differentiated HN2-5 cells, 5-HT$_{1A}$ agonists increased ERK phosphorylation and activity.[101] These and other studies suggest that the modulation of ERK may depend on neuronal origin, as well as maturation states.[102−106]

The Akt signaling pathway is also activated in 5-HT$_{1A}$ receptor-expressing cells and primary hippocampal neurons.[104,107,108] Activation of Akt by 5-HT$_{1A}$ receptors led to inactivation of GSK3β in hippocampal cultures,[104,109,110] an effect also observed in raphe cultures.[105] Recently, it has been suggested that the GSK3-regulating effects of 5-HT$_{1A}$ receptors are mediated by the PI3K/Akt signaling pathway.[111] Taken together, 5-HT$_{1A}$ autoreceptors and heteroreceptors have diverse intracellular signaling capabilities contributing to the complex regulation of the serotonin system, as well as neuronal networks modulated by serotonin.

■ 5-HT$_{1A}$ RECEPTORS IN DEVELOPMENT

Serotonin is a morphogenic factor,[112] and alteration of serotonin levels during early developmental windows has been shown to influence mood- and anxiety-related behavior in adult animals.[113−115] Thus, mapping and understanding factors that regulate the developmental trajectory of 5-HT$_{1A}$ receptor expression are important given that autoreceptors modulate serotonin release and heteroreceptors are widely expressed in emotion-related circuits, where they mediate the effects of released serotonin. In rodents, 5-HT$_{1A}$ receptors appear in early embryonic development. Using in situ hybridization and immunocytochemistry, 5-HT$_{1A}$ mRNA has been detected as soon as embryonic day (E) 12 and 5-HT$_{1A}$ receptor protein by E14 in neuronal cultures prepared from brain stem.[116] A surge in 5-HT$_{1A}$ mRNA levels in the brain stem occurs beginning on E13, with peak levels occurring at E15−16.[117] Developmentally related changes in 5-HT$_{1A}$ receptor expression also occur at postsynaptic sites. Transient expression is evident in the septum and preoptic region during embryonic development.[118] 5-HT$_{1A}$ expression occurs at high levels in the cerebellum during the first two postnatal weeks tapering off to near undetectable levels by postnatal day (P) 21.[119,120] In brain regions associated with the regulation of mood and anxiety, 5-HT$_{1A}$-receptor expression likewise exhibits complex patterns during development. In situ hybridization and [^{3}H]-8-OH-DPAT binding both indicate low 5-HT$_{1A}$ expression in the dentate gyrus granule cell layer of the hippocampus at E14.5, with levels gradually increasing during the first few postnatal weeks and reaching near adult levels by P13.[118−121]

Reports on the ontogeny of 5-HT$_{1A}$ receptors in the developing human brain, albeit fewer, are in agreement with those on rodents. In one study, [^{3}H]-8-OH-DPAT binding was used to examine 5-HT$_{1A}$ receptor expression from tissue acquired at different stages of gestation.[122] Although expression levels varied with respect to gestational age (16−22 weeks), the relative regional distribution of 5-HT$_{1A}$ receptors was similar across time points. The highest receptor densities occurred in subregions of the hippocampus and frontal cortex, where a surge in 5-HT$_{1A}$ expression was observed at 18−22 weeks of gestation resulting in levels 3−4 times higher than those reported in adults.[122] Others have used in situ hybridization to compare 5-HT$_{1A}$ receptor mRNA levels in human tissue collected at ∼28 weeks of gestation compared to 6−7 years of age.[123] Human fetal brain contained the highest 5-HT$_{1A}$ mRNA levels in raphe nuclei, cerebellum, and the CA1 and dentate gyrus regions of the hippocampus. When compared to later ages, only expression in the cerebellum showed dramatic changes, with mRNA levels being lower in children and undetectable in adults.[123,124] The latter is similar to the cerebellar expression pattern reported in rodents. Thus, 5-HT$_{1A}$-receptor expression undergoes tight temporal regulation and in some regions, brief emergence and disappearance, suggesting morphogenic influences, especially in areas of the brain involved in modulating anxiety levels in adults.

A few studies have investigated functional aspects of 5-HT$_{1A}$ receptors during development by means of electrophysiology or pharmacologic challenge. Electrophysiological recordings in the prefrontal cortex of rats indicated that 5-HT$_{1A}$ receptor-mediated hyperpolarization appears late in postnatal development between P16 and P19 corresponding temporally with increases in receptor protein expression.[118−120,125] In mice, 5-HT$_{1A}$-receptor mediated outward currents were not evident at P4 but were observed by P12.[126] 5-HT$_{1A}$ responses developed after the appearance of physiology characteristic of serotonergic neurons, which appeared to be fully developed by P12. 5-HT$_{1A}$ receptor-signaling pathways important for mediating developmental processes are complex. For example, 8-OH-DPAT-induced activation of the MAPK pathway, and specifically ERK1/2 kinases, requires different PKC isozymes to regulate distinct developmental processes (e.g., cell division

versus synaptic activity/strengthening) at P6 versus P15.[127] More work will be needed to understand functional changes in 5-HT$_{1A}$ mediated pre- and postsynaptic responses during postnatal development, particularly in terms of critical developmental windows important for shaping and determining anxiety-related behavior later in life.

5-HT$_{1A}$ RECEPTORS IN MOOD AND ANXIETY

Mechanisms of Antidepressants. 5-HT$_{1A}$ autoreceptors play an important role in regulating serotonergic activity through feedback inhibition pathways. As such, the involvement of 5-HT$_{1A}$ receptors in the mechanism of action of antidepressants has been widely investigated, and literature supporting a role for this receptor population in the delayed efficacy of antidepressants has evolved. 5-HT$_{1A}$ autoreceptors (and possibly heteroreceptors) limit increases in extracellular serotonin levels induced by serotonin selective reuptake inhibitors (SSRIs). Even after chronic SSRI treatment, 5-HT$_{1A}$ autoreceptors maintain some control over serotonin release.[128−132]

The delayed efficacy of SSRIs has been partially attributed to the need for desensitization of 5-HT$_{1A}$ autoreceptors in the raphe nuclei, enabling firing rates of serotonergic neurons to overcome inhibition.[128,133−137] However, only ∼50% of studies in rodents show increased extracellular serotonin after chronic administration of serotonin reuptake inhibiting antidepressants.[138] In this context, concomitant administration of 5-HT$_{1A}$ receptor antagonists with SSRIs has been hypothesized to hasten or potentiate changes in serotonin levels to improve clinical efficacy.[54,139] The ability of the partial 5-HT$_{1A}$ antagonist, pindolol, to accelerate antidepressant clinical efficacy has been investigated in patients with major depressive disorder. Meta-analyses suggest that pindolol administered in combination with SSRIs augments and accelerates symptomatic improvement after 2 weeks of treatment specifically in patients without prior history of treatment.[140−142]

However, not all findings support a role for 5-HT$_{1A}$ autoreceptor desensitization and its effects to accelerate SSRI treatment. For example, administration of pindolol in combination with SSRIs to patients with treatment resistant depression or extensive treatment histories does not hasten or produce symptom amelioration.[143,144] Human studies examining the role of 5-HT$_{1A}$ receptors in the treatment and etiology of major depressive disorder indicate that sensitivity to receptor signaling after administration of agonists are complicated based on reports of reduced receptor number and binding, as well as genetic influences.[145] Additionally, mechanisms of autoreceptor desensitization are not clear and may differ depending on the antidepressant administered. For example, chronic fluoxetine results in desensitization of autoreceptors, which is associated with a reduction in receptor stimulated [^{35}S]GTPγS binding.[146−149] However, G-protein coupling is not altered in association with administration of the SSRI sertraline, indicating that antidepressants differ with regard to mechanisms of 5-HT$_{1A}$ desensitization.[146]

In addition to conflicting findings regarding 5-HT$_{1A}$ autoreceptor desensitization in clinical studies, desensitization occurs in animal models of depression generated via chronic stress paradigms.[150−154] 5-HT$_{1A}$ autoreceptors and heteroreceptors are also desensitized in serotonin transporter knockout mice in association with a phenotype characterized by enhanced anxiety.[155−158] Together, these studies highlight the complex regulation of 5-HT$_{1A}$ pathways, such that desensitization may be common to both the treatment and precipitating etiological factors associated with major depressive disorder.

Animal Models of 5-HT$_{1A}$ Disruption. In light of data suggesting a role for 5-HT$_{1A}$ receptors in mediating antidepressant responses in humans, it is logical to suspect that these receptors also function in the neurocircuitry and pathophysiology of emotion-related behavior. Genetic manipulation of the murine *Htr1A* gene has been carried out to study the behavioral effects of receptor under- or overexpression. In both cases, the majority of data point to a role for 5-HT$_{1A}$ receptors in anxiety-related behavior. Table 1 in the Supporting Information provides a comprehensive summary of the literature to date focused on anxiety- and depression-like behaviors, and learning and memory in animal models of altered 5-HT$_{1A}$ expression. Taken together, these studies provide convincing evidence that global reductions in 5-HT$_{1A}$ receptor expression lead to increased anxiety-related behavior in adult animals across different strains of mice and behavior test paradigms.

The first reports on mice with reduced 5-HT$_{1A}$ expression appeared simultaneously in 1998. Three separate laboratories produced constitutive 5-HT$_{1A}$ knockout mice, each in a different background strain (Supporting Information Table 1).[159−161] Consistent changes in behavior were observed in tests for anxiety-related behavior associated with conflict in novel environments, including exploration in the center of the open field or the open arms of the elevated plus maze. Changes in behavior were more consistently replicated across tests in male versus female mice. In terms of depression-like behaviors, mice with reduced 5-HT$_{1A}$ expression displayed reduced immobility in the forced swim[160,161] and tail suspension tests.[159] However, interpretations of these behavioral changes were not in agreement. Some authors perceived decreased immobility as an increased stress response,[160] while others took a more traditional view of reduced immobility[162] as indicative of decreased learned helplessness/behavioral despair or an increased antidepressant-like response.[159,160]

Following these initial reports, others confirmed increased anxiety-like behavior in 5-HT$_{1A}$ knockout mice when presented with conflict situations (see Supporting Information Table 1 for a full list of references). Findings also included modestly enhanced fear responses to stressful stimuli such as foot shock.[163−166] In terms of learning and memory, mice with reduced 5-HT$_{1A}$ expression displayed deficits in hippocampal-dependent learning indicated by increased latencies and path lengths to find the hidden platform in the Morris water maze.[167,168] As opposed to mice with constitutive deletion of 5-HT$_{1A}$ receptors, mice with developmentally limited overexpression of 5-HT$_{1A}$ heteroreceptors in dentate gyrus and cortex also displayed reduced anxiety in novel, conflict environments.[169] By contrast, mice with permanent overexpression failed to show changes in anxiety-like behaviors.[170] Similar to 5-HT$_{1A}$ knockout mice, transient 5-HT$_{1A}$ overexpression resulted in deficits in hippocampal-dependent learning and memory in the Morris water maze.[171] Deficits were less pronounced or absent in permanent overexpressing mice.[172] Information pertaining to changes in learning and memory after 5-HT$_{1A}$ receptor manipulation is reviewed in detail elsewhere.[172,173]

Recently, studies have been carried out to delete specific subpopulations of 5-HT$_{1A}$ receptors enabling the differentiation of pre- versus postsynaptic behavioral effects.[174] When 5-HT$_{1A}$

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autoreceptors were selectively inactivated, mice exhibited increased anxiety-like behavior similar to constitutive knockout mice. These findings highlight the importance of raphe 5-HT_{1A} receptors in mediating anxiety responses. By contrast, when 5-HT_{1A} heteroreceptors were specifically targeted, normal anxiety-like behavior was observed; however, increased depression-like behavior was observed in the forced swim test.[174] Increased anhedonic behavior related to reduced consumption of palatable food has also been observed in mice with 5-HT_{1A} heteroreceptor knockout. The latter findings on depression-related behavior illustrate an interesting dichotomy since mice with constitutive deletion of 5-HT_{1A} auto- and heteroreceptors show *decreases* in depression-like behavior (see Supporting Information Table 1). Thus, the synergistic effects of genetically inactivating auto- and hetero 5-HT_{1A} receptors cannot be predicted by studying knockout of either receptor population in isolation.

In addition to mice with complete loss of 5-HT_{1A} autoreceptors, mice with 30% reductions in 5-HT_{1A} autoreceptor expression have been generated.[175] These mice display potentiated responses to the administration of fluoxetine as indicated by increased dialysate serotonin levels. These findings are important in the context of human *HTR1A* gene polymorphisms, including the C(−1019)G *HTR1A* single nucleotide polymorphism,[176−178] which is hypothesized to affect the expression and function of 5-HT_{1A} receptors and to contribute to the high numbers of antidepressant nonresponders.[179]

NEW PERSPECTIVES ON 5-HT_{1A} AUTORECEPTORS

Networks and 5-HT_{1A} Inhibitory Function. It is widely accepted that 5-HT_{1A} receptors located on serotonergic neurons participate in autoinhibition. However, a more complex picture of inhibitory function than simple one-to-one regulation of serotonin cell firing is emerging. Serotonin neurons are anatomically heterogeneous and their projections to the forebrain are topographically organized.[180−183] Furthermore, distinct, reproducible patterns of serotonin neuron activation within the raphe nuclei can be seen in response to specific external stimuli, suggesting that anatomical topography underlies functional topography.[182,184] Additionally, microdialysis studies examining extracellular serotonin levels after the application of various stressors have supported the idea of defined network patterns of serotonin neurons such that stress-induced changes in serotonin levels are stressor- and region specific.[185] These observations suggest that feedback inhibitory pathways might work to control serotonin-network activity. In one model, raphe serotonin neurons exhibit autonomous feedback such that groups of functionally similar serotonergic neurons regulate themselves in a homeostatic manner (Figure 1C).[180]

Nonautonomous feedback has also been suggested in which crosstalk between distinct groups of serotonin neurons provides "lateral inhibition" influencing patterns of activation (Figure 1C).[180] Along these lines, recent work by Commons and Sperling has demonstrated complementary patterns of activation of serotonergic neurons after exposure to and withdrawal from nicotine, which are different and reciprocally switched after 5-HT_{1A} receptor blockade.[181] These findings suggest that endogenous feedback inhibition provided by 5-HT_{1A} receptors might be regionally organized and depend on behavioral states. While these observations do not exclude an autoregulatory function, they raise the possibility that 5-HT_{1A} receptors might also operate in a nonautonomous fashion to mediate communication between different groups of serotonin neurons, thus suggesting that 5-HT_{1A} receptors are involved in a regional form of autoregulation between different raphe subfields. These studies are consistent with anatomical studies showing that there are many interconnections between the different raphe nuclei[180] and axon collaterals of serotonin neurons travel for some distance within the dorsal raphe nuclei.[186]

There are also a number of distinct serotonin subsystems with unique genetic programming and functions.[187] Recent studies have shown that, in raphe nuclei, there are at least three different serotonin cell-types grouped by anatomical, physiological, and molecular characteristics, and their distribution transcends the traditional anatomical classification of raphe subfields. Furthermore, forebrain regions receiving serotonergic projections are innervated by serotonin neurons with distinct characteristics, forming a highly organized circuit.[188] Therefore, identifying and understanding functionally specific axon collaterals within the raphe that are involved in controlling emotional behaviors is likely to be an important future direction of research.

FUTURE PROSPECTS

Targeting Specific Receptor Populations. The evolving distinctions between the specific and diverse roles for 5-HT_{1A} auto- versus heteroreceptors and the manner in which different populations of neurons expressing 5-HT_{1A} receptors elicit control over serotonergic tone is now shifting away from simplified views centered on autonomous autoreceptor-mediated feedback inhibition. Classical definitions of autoreceptors, which have long been associated with controlling serotonergic firing rates via feedback inhibition, remain an important functional property of these receptors. Yet, rather than one-to-one associations, emerging findings point to the idea that inhibitory regulation is also more complex and might operate at several levels that involve multiple pathways and/or networks that influence neighboring circuits.

As the rich complexity of 5-HT_{1A} receptor organization and function continues to be uncovered, optimizing treatment strategies for mood and anxiety disorders by preferentially targeting different 5-HT_{1A} receptor populations or networks to produce therapeutic effects should become possible. For example, the novel 5-HT_{1A} agonist, F15599, has been shown to reduce immobility in the forced swim test[189] and to promote these effects primarily through activation of 5-HT_{1A} heteroreceptors localized in the frontal cortex.[106] These findings support the idea that in addition to 5-HT_{1A} autoreceptor desensitization following antidepressant treatment, increased 5-HT_{1A} heteroreceptor activity occurs to promote antidepressant efficacy.[190−193] Furthermore, in support of the roles of 5-HT_{1A} autoreceptors in mood and anxiety-related behavior, recent advances using siRNA to silence 5-HT_{1A} autoreceptor expression have been shown to ameliorate immobility associated with learned helplessness and to augment fluoxetine-induced increases in serotonin levels in postsynaptic regions.[194,195]

5-HT_{1A} Receptors: A View of the Future. The serotonin system, and 5-HT_{1A} receptors in particular, exhibit properties that continue to challenge and enlarge our understanding of receptor function. In addition to direct autonomous inhibition, evidence now exists for indirect inhibition of raphe serotonergic neurons arising from a mPFC-DRN pathway. It will be

informative to sort out whether direct and indirect pathways work independently or synergistically to limit serotonin release in the mPFC. Moreover, the actions of serotonin might be coordinated across different brain regions as part of a global circuitry via lateral inhibition within and across subpopulations of raphe neurons, some of which have different developmental origins and genetic lineages. Thus, a picture of 5-HT_{1A} receptor-mediated control of emotion-related behavior via coordination of brain-wide networks is coming to light. Still, additional work will be needed to uncover precise interactions between different parts of this network, hierarchical principles of 5-HT_{1A} receptor function, and early life sequencing with regard to lasting consequences for network development.

Many animal models of altered 5-HT_{1A} receptor expression have been created. Taken together, studies on these models highlight two important aspects of 5-HT_{1A} receptors in regard to anxiety-related behavior. First, most studies point to 5-HT_{1A} receptors, particularly during postnatal development, as key regulators of anxiety (see Supporting Information Table 1). By contrast, pharmacologic inhibition or genetic manipulation of 5-HT_{1A} receptors in adult animals fails to produce anxiogenic behavior.[196,197] Second, unraveling the significance of 5-HT_{1A} auto- versus heteroreceptors in regard to establishing baseline anxiety behavior is important. Null 5-HT_{1A} mutant mice in which 5-HT_{1A} heteroreceptors were ectopically overexpressed during development[169] or where 5-HT_{1A} receptor expression was restored in forebrain regions, for example, hippocampus, cortex, and striatum,[196] exhibit reversal or rescue of increased anxiety behavior, respectively. However, the importance of heteroreceptors in gain-of-function experiments has been questioned by recent tissue-specific conditional knockout strategies where 5-HT_{1A} autoreceptors, but not heteroreceptors, have been shown to be critical components for establishing normal levels of anxiety.[174] As additional information on the specific roles of different 5-HT_{1A} receptor subpopulations and their influence over emotion-related behaviors during various timeframes become clear, avenues for novel treatment strategies for mood and anxiety disorder should become evident.

Further, as we sort out which 5-HT_{1A} receptor inhibitory circuits play key roles in shaping specific types of behavior, these are also expected to become targets for the development of more selective and, hopefully, more effective therapeutics. Recent findings have shown that different populations of 5-HT_{1A} receptors are coupled to different/multiple intracellular signaling pathways. This suggests the possibility of developing allosteric modulators or other types of small-molecule drugs that modify specific intracellular signaling pathways in cases where a particular type of receptor is coupled to more than one pathway in the same cell type or to different Gα subunits in different cells types.

Finally, the serotonin system remains unique among known neurotransmitter systems in that it is the only system identified as having two molecularly distinct autoreceptors. In addition to 5-HT_{1A} receptors, serotonergic function is regulated by 5-HT_{1B} autoreceptors, which are expressed presynaptically on serotonin axon terminals, in addition to postsynaptic axonal localization associated with dopaminergic, GABAergic, and glutamatergic systems.[198] Thus, both 5-HT_{1A} and 5-HT_{1B} receptors function as autoreceptors and heteroreceptors. It is tempting to think that 5-HT_{1B} receptors might exhibit complexity similar to 5-HT_{1A} receptors in terms of multiple inhibitory circuits or hierarchical organization. Perhaps, continued investigation of 5-HT_{1A} (and 5-HT_{1B}) receptors, as well as other receptor subtypes that function both as auto- and heteroreceptors, for example, dopamine D2 and noradrenergic alpha2 receptors, will reveal additional modes of regulatory feedback and network organization. Nonetheless, it appears that recent advances in understanding 5-HT_{1A} receptor function lead the way in terms of extending and expanding our thinking as to how behavioral circuits are organized and controlled by a specific receptor subtype. They also provide exciting new opportunities for drug discovery and development, particularly for the treatment of mood and anxiety disorders.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Table detailing behavior phenotypes in models of 5-HT_{1A} receptor disruption or overexpression. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(E.D.L.) Mailing address: Department of Psychiatry, 1051 Riverside Dr. Box 87, Columbia University, New York, NY 10032. E-mail: el367@columbia.edu. Phone: 212-543-5266. (A.M.A.) Neuroscience Research Building, Room 545, 635 Charles E. Young Dr. S, Box 957332, Los Angeles, CA 90095-7332. E-mail: aandrews@mednet.ucla.edu. Phone: 310-794-9421.

Author Contributions

⊥These authors contributed equally.

Notes

The authors declare no competing financial interest.

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