The Serotonin-1A Receptor in Anxiety Disorders

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The serotonin system plays an important role in the neural processing of anxiety. The involvement of the main inhibitory serotonergic receptor, the serotonin-1A (5-HT1A) subtype, in dysfunctional forms of anxiety has been supported by findings from a wide range of preclinical research and clinical trials, including treatment studies, genetic research, and neuroimaging data. The following article summarizes preclinical results with a focus on 5-HT1A receptor knockout and transgenic mice as genetic models of anxiety. Behavioral, autonomic, and endocrinological changes in these mice are reported. This article also presents genetic polymorphisms in humans associated with increased anxiety scores and pharmacological data focused on 5-HT1A receptor agonists and antagonists. Furthermore, molecular neuroimaging results are presented. Recent positron emission tomography (PET) studies have reported reduced 5-HT1A receptor binding in patients with panic disorder and social anxiety disorder, but not in posttraumatic stress disorder. In healthy subjects, increased anxiety scores might be associated with lower 5-HT1A receptor binding. This overview of preclinical and clinical data provides strong evidence for the key role of the 5-HT1A receptor in the serotonergic dysregulation of anxiety disorders.

Key Words: Anxiety, 5-HT1A, knockout mice, neuroimaging, serotonin, SSRIs

Brain serotonin (5-HT) plays a major role in a number of physiological processes and pathological conditions. Serotonin neurotransmission is involved in the regulation of mood, impulse control, sleep, vigilance, eating, libido, and cognitive functions, such as memory and learning. In addition, serotonin is important in the modulation of anxiety and fear, as well as impulsiveness in suicidal and other violent acts (1,2). These effects are mediated by at least 14 different 5-HT receptors (3). Among them, the serotonin-1A (5-HT1A) receptor in particular is thought to play an important role in the etiology of anxiety disorders, supported by the fact that partial 5-HT1A receptor agonists are anxiolytics (4).

Nonpsychotic and nonorganic anxiety is part of the following disorders: phobic anxiety disorders, general anxiety disorder (GAD), panic disorder (PD), obsessive-compulsive disorder (OCD), reaction to severe stress as acute stress reaction, and posttraumatic stress disorder (PTSD). Pathological harm avoidance, induced by conflict and fear, is a dimension of anxiety-related responses and may also be associated with increased 5-HT functional activity (5–7). All of these disorders have common behavioral and physiological characteristics that respond to similar pharmacological treatment. Selective serotonin reuptake inhibitors (SSRIs) have become the first-line treatment for anxiety disorders. They act by selectively blocking the reuptake of 5-HT following its release from neurons, thereby changing 5-HT neurotransmission in the brain, including binding on the 5-HT1A receptor (8,9).

Due to the high density of the 5-HT1A receptor subtype in several cortical and subcortical areas, this receptor is considered the major inhibitory serotonergic receptor (10). See Figure 1 for the distribution of 5-HT1A receptors in the human brain. The 5-HT1A receptor is expressed in high concentration in limbic, temporal, and prefrontal cortices, while having low density in the primary sensory areas. It is not yet certain how 5-HT1A alterations in different human brain areas are specifically associated with dysfunctions in anxiety processing. However, the topology of 5-HT1A alterations is a relevant factor. Given its broad distribution within the cortex, it is important to consider that 5-HT1A plays a role not only in anxiety and affective disorders, but also in the regulation of a variety of physiological states and behaviors, including fear, aggression, and impulsivity, as recently demonstrated by Witte *et al.* (11). Several human positron emission tomography (PET) studies showed that the lower tracer binding of the receptor observed in patients with psychiatric disorders, when compared with control subjects, was limited to distinct regions of the brain (12). Brain 5-HT1A receptors are located both presynaptically and postsynaptically. Presynaptic 5-HT1A receptors are present on serotonergic neurons in the dorsal and medial raphe nuclei and act as somatodendritic autoreceptors. The activation of these receptors by 5-HT causes a reduction in the firing rate of the serotonergic neurons and suppression of 5-HT synthesis, 5-HT turnover, and 5-HT release in projection areas. Postsynaptic 5-HT1A receptors are mainly located on glutamatergic and GABAergic (gamma-aminobutyric acid) pyramidal neurons in limbic regions and in the frontal and entorhinal cortices (13–15). They modulate serotonergic sensitivity and are involved in emotional and cognitive processes (10,16).

This overview aims to present the most important literature currently available on clinical and preclinical findings demonstrating the pivotal role of the 5-HT1A receptor in anxiety disorders.

Results in Animal Studies

Previous results in rats (17,18), knockout mice (19), and nonhuman primates (20) showed the key role of the 5-HT1A receptor in the modulation of behavioral correlates, anxiety and fear, that may have counterparts to anxiety and fear in humans (Table 1).

In our overview, we focus on transgenic and knockout mice models of the 5-HT1A receptor, which represent a genetic model of anxiety and are useful in explaining pathogenetic pathways leading to this disorder (21). A significant increase in the anxiety level and anxious behavior is present not only in homozygote but also in heterozygote 5-HT1A receptor knockout mice, indicating that a partial receptor deficit is sufficient to elicit the phenotype. Therefore, receptor downregulation may be an important risk factor in psychiatric disorders. Tables 1, 2, and 3 summarize preclinical results described in detail below.

Behavioral Features in 5-HT1A Receptor Knockout Mice

Three knockout lines were generated from different genetic backgrounds and tested under similar conditions to evaluate fear,

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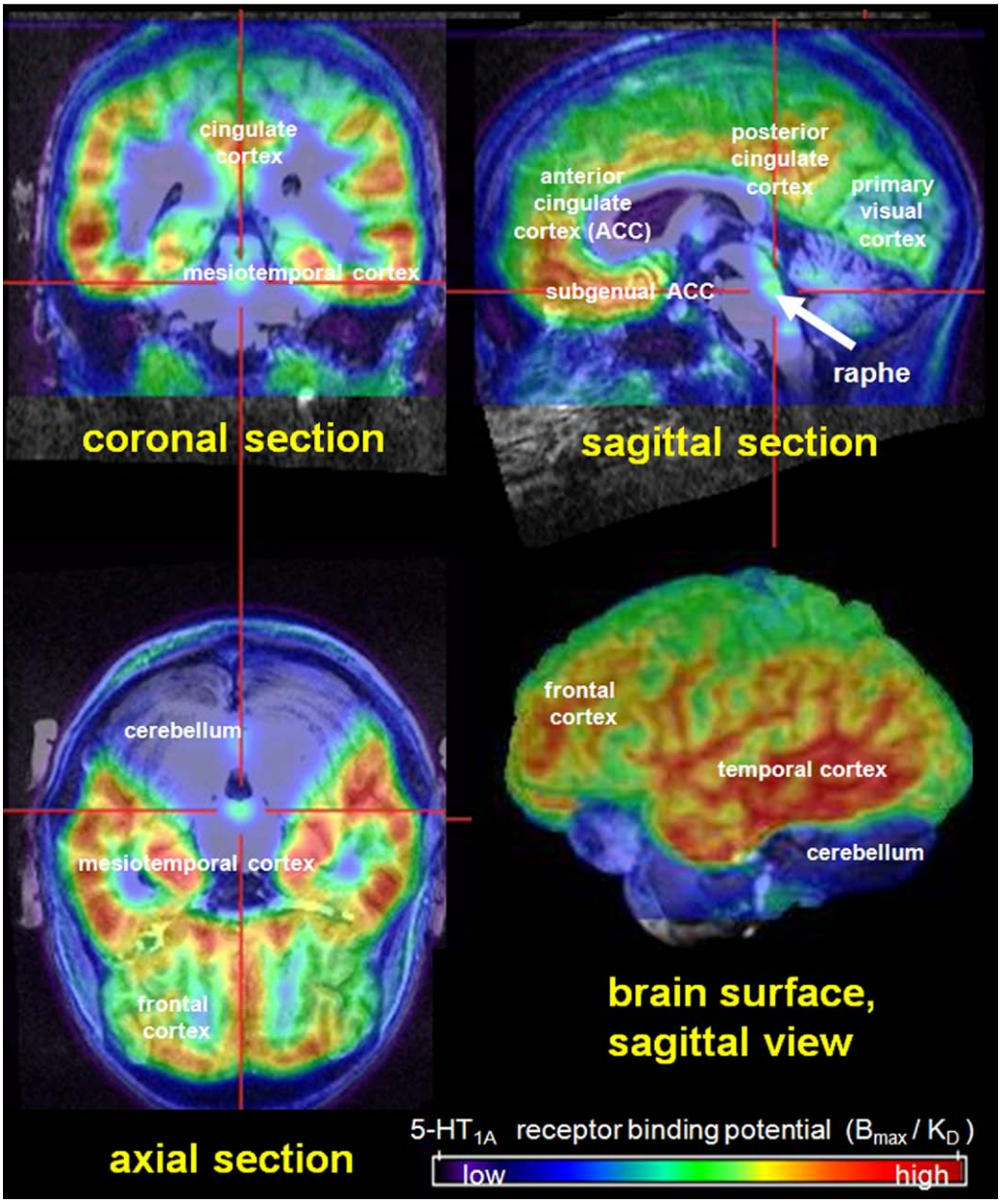

Figure 1. Serotonin-1A receptor distribution in the healthy human brain. The color table indicates the 5-HT1A receptor binding potential superimposed on magnetic resonance images (triplanar sections with coronal, sagittal, and axial views; brain surface). The binding was measured using positron emission tomography and the highly selective and specific radioligand [*carbonyl*-^{11}C]WAY-100635. Red crosshairs indicate the raphe nuclei region expressing presynaptic 5-HT1A autoreceptors on serotonergic neurons. The postsynaptic 5-HT1A receptors in cortical regions are mainly expressed on glutamatergic and GABAergic pyramidal neurons. High 5-HT1A receptor densities (red) can be found in limbic areas including the hippocampus and cingulate cortex and in prefrontal and temporal cortices. Low densities are expressed in the primary visual cortex and the primary motor cortex. 5-HT1A, serotonin-1A.

avoidance, conflict, and stress responsiveness (22–24). Mice with the genetic deletion of the 5-HT1A receptor were shown to be more fearful in a number of behavioral conflict tests.

Transgenic Mice Models

As the 5-HT1A receptor is expressed postsynaptically on glutamatergic and GABAergic neurons and presynaptically on serotonergic neurons in the raphe nuclei, it is of major interest to know whether a presynaptic or postsynaptic receptor pool is required to maintain a normal level of fear and anxiety in mice.

Gross *et al.* (25) created a mouse with a double transgenic line, otherwise known as the "rescue" line. This mouse exhibits postsynaptic 5-HT1A receptors that approximately imitate the wild-type receptor pattern in the forebrain; however, presynaptic receptors are not expressed in the raphe nuclei of the brainstem.

Rescue mice demonstrate wild-type levels of anxiety, showing a reversal of the anxiety phenotype of knockout mice. This means that 5-HT1A receptors in the forebrain are able to restore normal anxiety behavior in knockout background, suggesting an important role for forebrain receptors in regulating anxiety

Table 1. 5-HT1A and Transgenic Mice as Genetic Models of Anxiety Disorders

Behavioral Features	Knockout 5-HT1A$^{-/-}$	Heterozygote 5-HT1A$^{+/-}$	Overexpression 5-HT1A Transgenic	Rescue-Turned Off in the Adult	Rescue-Turned Off During Development	References
Anxiety-Related Responses	↑	↑	↓	=	↑	22, 23, 24, 25, 28, 37, 91
Harm Avoidance	↑	↑	↓	=	↑	22, 23, 24, 25, 28, 37, 91
Aggression	=	=	↑	n.t.	n.t.	91, 90
Fear Conditioning	↑	n.t.	n.t.	n.t.	n.t.	92
Exploratory Activity	↓	↓	↑	=	↓	22, 23, 24, 25, 28, 37, 91
Learning Deficit	↑	n.t.	n.t.	n.t.	n.t.	90
Freezing Response After Shock	↑	n.t.	n.t.	n.t.	n.t.	92

5-HT1A, serotonin-1A; ↑, significant increase; ↓, significant decrease; =, changes were not significant; n.t., not tested.

behavior in wild-type mice. Gross *et al.* (25) studied the conditional nature of the receptor in rescue mice to assess the effect of 5-HT1A receptors during development and adulthood in the rescue phenotype. Test results indicated that deletion of the 5-HT1A receptor in mice produces a robust anxiety-related phenotype and that this phenotype in 5-HT1A knockout mice is caused by the absence of the receptor at a critical period of postnatal development, whereas the knockout of 5-HT1A in adulthood does not affect anxiety. Even more significantly, these findings support the idea of a central role for serotonin in the early development of neurocircuits mediating emotion (26,27).

To further analyze the role of the 5-HT1A receptor in anxiety-like behavior, transgenic mice overexpressing this receptor subtype were generated (28). The expression of the 5-HT1A receptor protein was transiently increased during postnatal development. Interestingly, transgenic mice showed elevated serotonin values in the hippocampus and striatum.

Several studies have shown that steroid hormones such as cortisol and estrogenes are potent modulators of 5-HT1A receptor expression (29). While maternal stress during pregnancy changes the hormonal condition of the fetus, maternal behavior during the early postnatal phase influences the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal axes of the progeny (30,31). Given the sensitive periods in the maturation of the serotonergic system, these environmental factors may have life-long effects on serotonergic neurotransmission and 5-HT1A receptor expression causing vulnerability to stress in adulthood. These critical findings should be integrated into future research on humans to investigate whether multifactorial disorders may result from variations in a small number of genes, with varying effects dependent on the exposure to environmental risk factors like malfunctions of the maternal stress systems during pregnancy or stressful life events in early childhood (32,33). Also, the association of genetic liability with personality traits like neuroticism, which seem to increase the likelihood of the development of psychiatric disorders, should be considered (34,35).

Autonomic Changes in 5-HT1A Receptor Knockout Mice

Autonomic manifestations of anxiety, such as increased blood pressure, heart rate, and elevated body temperature, are experienced by anxiety patients. These factors were measured in animal models to determine anxiety levels (36–38). Pattij *et al.* (36) observed that in a novel environment, the heart rate of 5-HT1A receptor knockout mice was twice that of wild-type control animals. Body temperature also increased more significantly in knockout animals. Baseline values of heart rate and body temperature showed no differences between the groups.

Stress Responsiveness and the Hypothalamic-Pituitary-Adrenal System

Increased stress responsiveness was observed in knockout mice when compared with wild-type mice in forced swim tests and tail suspension tests. Knockout mice, when placed in water or suspended by the tail, show a stress-induced increase in mobility (22–24). When using aversive stimuli to induce freezing, higher rates of stress and anxiety were displayed by knockout mice (39,40).

Stress and anxiety disorders are frequently accompanied by the activation of the HPA system. The release of corticosterone by the adrenal gland was shown partially reduced in 5-HT1A receptor knockout mice (39,41). Both glucocorticoid administra-

Table 2. Behavioral Conflict Tests on 5-HT1A Knockout and Transgenic Mice

Conflict Tests, Anxiety Paradigms	Knockout 5-HT1A$^{-/-}$	Heterozygote 5-HT1A$^{+/-}$	Overexpression 5-HT1A Transgenic	Rescue-Turned Off in the Adult	Rescue-Turned Off During Development	References
Home Cage Activity	=	=	↓	n.t.	n.t.	22, 28
Light-Dark Test	↓	n.t.	n.t.	n.t.	n.t.	90
Open Field	↓	↓	=	=	↓	22, 23, 24, 25, 28, 37
Elevated-Plus Maze	↓	↓	↑	=	↓	22, 23, 24, 25, 28, 37
Novel Object	↓	=	n.t.	n.t.	n.t.	22
Tail Suspension	↓	↓	n.t.	n.t.	n.t.	22
Forced Swim Test	↑	↑	n.t.	n.t.	n.t.	23, 24
Morris Water Maze	↑	n.t.	n.t.	n.t.	n.t.	90
Novelty Suppressed Feeding	↓	n.t.	n.t.	=	↓	90, 25
Novel Environment	↑	n.t.	n.t.	n.t.	n.t.	25, 37
Freezing Response	↑	n.t.	n.t.	n.t.	n.t.	90

5-HT1A, serotonin-1A; ↑, significant increase; ↓, significant decrease; =, changes were not significant; n.t., not tested.

Table 3. Physiological and Autonomic Changes in 5-HT1A Knockout and Transgenic Mice

Physiological Features, Autonomic Changes	Knockout 5-HT1A$^{-/-}$	Heterozygote 5-HT1A$^{+/-}$	Overexpression 5-HT1A Transgenic	References
Heart Rate	=	=	n.t.	36
Basal Body Temperature	=	=	↓ (male)	36, 28
Stressed-Induced Tachycardia	↑	=	n.t.	36, 37
Stressed-Induced Hyperthermia	↑	=	n.t.	36, 25, 37, 38
Stress Responses	↑	↑	n.t.	38, 38, 40, 42
ACTH, Prolactin, Corticosterone, Adrenaline Levels	↑	n.t.	n.t.	45
Glucose Level	↑	n.t.	n.t.	45
Serotonin Level	↑	n.t.	n.t.	45

5-HT1A, serotonin-1A; ACTH, adrenocorticotropic hormone; ↑, significant increase; ↓, significant decrease; =, changes were not significant; n.t., not tested.

tion and chronic stress have also been shown to result in downregulation of 5-HT1A receptor density and messenger RNA (mRNA) levels in the hippocampus (42,43), where 5-HT1A receptor expression is inhibited by corticosteroid receptor stimulation. In contrast, 5-HT1A receptors in the raphe nuclei seem unaffected by circulating corticosteroids (44).

Pharmacological Effects on the 5-HT1A Receptor

Pharmacological tests on knockout mice are a powerful tool in understanding both the consequences of the deletion of 5-HT1A receptors and the effects of pharmacological treatment on this receptor (Table 1 in Supplement 1). Anxiety disorders are commonly treated with benzodiazepines that bind to $GABA_A$ receptors. The anxiolytic activity of benzodiazepines is dependent on the genetic background of knockout mice. It was shown that 5-HT1A receptor knockout mice display benzodiazepine-resistant anxiety (41). In contrast to these mutants, receptor-deficient mice of the 129sv and C57B16 genetic backgrounds responded to benzodiazepines (37). This data clearly demonstrates that benzodiazepine resistance is mediated by an interaction between the 5-HT1A receptor and one or more unknown genes and their modification in the $GABA_A$ complex is independent of the anxiety phenotype.

Serotonin-1A receptors modulate the anxiolytic effects of SSRIs. In several investigations, pharmacological blockades in 5-HT1A receptor knockout mice were introduced and the impact on regulation of synaptic serotonin was studied, showing knockout mice to have increased fluoxetine-induced dialysate serotonin content in various brain regions (45,46). Knobelman *et al.* (46) presented results, indicating the significant role of the receptor in regulating 5-HT1A receptor-mediated release in the striatum and other brain regions innervated by neurons of the medial raphe nucleus. Similarly, Parson *et al.* (45) described a larger disinhibition of serotonin release in the frontal cortex than in the ventral hippocampus in knockout mice following treatment with fluoxetine.

Pindolol is a β_{1-2} adrenergic receptor antagonist with a putative antagonistic action on 5-HT1A receptors and a greater occupation at somatodendritic 5-HT1A receptors than at postsynaptic receptors. While the clinical benefits of SSRIs are only evident after 4 to 6 weeks of treatment, pindolol seems to speed up this process. This effect may be mediated by somatodendritic 5-HT1A receptors. Guilloux *et al.* (47) studied the mechanism of pindolol and the antidepressant effect of a combination with paroxetine in 5-HT1A knockout mice. They found no effect on 5-HT1A autoreceptors. The blockade of paroxetine-induced antidepressant- and anxiolytic-like effects may be strongly associated with its binding to other neurotransmitter receptors.

The effects of selective 5-HT1A receptor agonists and partial agonists were investigated in detail in rodents (48). They cause a dose-dependent anxiolytic effect that correlates with the inhibition of serotonergic neuron firing, the decrease of 5-HT release, and the reduction of 5-HT signaling at postsynaptic target receptors. Blocking of the negative feedback by selective 5-HT1A receptor antagonists, such as WAY-100635, raises the firing level of the serotonergic neurons but has no obvious effects on 5-HT neurotransmission or behavior (49), while the combination with SSRIs augments the rise in serotonin levels in terminal regions. The activation of presynaptic 5-HT1A receptors provides the brain with an autoinhibitory feedback system controlling serotonin neurotransmission. Increased anxiety-related behavior may be associated with increased serotonin, resulting from a dysregulated negative feedback function in 5-HT1A autoreceptors (50). This mechanism is supported by recent theoretical models of fear and anxiety, primarily based on pharmacological data. The long-term reduction in serotonergic impulse flow to septohippocampal and other limbic and cortical areas involved in the control of anxiety may explain the anxiolytic effects of ligands with selective affinity for the 5-HT1A receptor in animal models of anxiety-related behavior. This is based on evidence that 5-HT1A agonists (8-OH-DPAT) and antagonists (WAY-100635) have anxiolytic or anxiogenic effects, respectively (51). The effects of 5-HT1A agonists injected centrally vary according to brain regions. Injections into areas such as the hippocampus and amygdala produce anxiogenic effects; however, when 5-HT1A agonists are injected into the dorsal or median raphe nuclei, anxiolytic effects can be observed. This evidence suggests that the postsynaptic 5-HT1A receptors and the 5-HT1A autoreceptors have opposite effects in the regulation of anxious behavior. Blier *et al.* (52) suggested that therapeutic effects of antidepressants are the result of 5-HT1A autoreceptor downregulation during chronic treatment without an alteration in the postsynaptic 5-HT1A receptors. Consequently, the stimulation of postsynaptic 5-HT1A receptors seems to be axiogenic, while the activation of 5-HT1A autoreceptors may induce anxiolytic effects via suppression of serotonergic neuronal firing. This, in turn, results in attenuated serotonin release. To confirm this hypothesis in humans, further knowledge of the status of the 5-HT1A receptors must be gained. Further details can be found in Supplement 1.

Results in Human Studies

Pharmacological Effects on the 5-HT1A Receptor in Anxiety Disorders

The efficacy of medications that increase the synaptic availability of serotonin has been shown consistently in clinical studies (53). Selective serotonin reuptake inhibitors may increase anxiety during the initial phase of treatment, a phenomenon that indicates the possible oversensitivity of serotonin postsynaptic receptors (54).

Neuropharmacological challenge studies with ipsapirone (a selective 5-HT1A receptor agonist) have been conducted to evaluate 5-HT1A receptor-related functions in patients with various affective and anxiety disorders (55-59). The 5-HT1A challenge studies by Broocks *et al.* (55,56), who observed patients with PD/agoraphobia, demonstrated that effective treatment has varying effects on the psychological, neuroendocrinological, and temperature responses to ipsapirone, as it induces cortisol secretion, increases anxiety, and causes other psychopathological symptoms, as well as lowering body temperature. Challenges were performed using ipsapirone and placebo in patients before and after 10 weeks of treatment with clomipramine.

Serotonin-1A receptor antagonists, such as pindolol, have the capacity to speed up the antidepressant effect of SSRIs by interrupting 5-HT1A autoreceptor inhibition of cell firing that occurs early in the treatment (60). There is some promising control data on the role of pindolol augmentation in OCD (61). Markovitz *et al.* (62) reported modest benefits in an open trial on OCD patients in which 9 out of 11 patients reported a beneficial effect.

Buspirone showed no significant effect in the treatment of PD (63–65). Ipsapirone, is possibly effective in the treatment of GAD (66); however, acute administration of ipsapirone causes panic attacks (55). Lesch (67) explored the sensitivity of the 5-HT1A receptor in PD and investigated hypothermic, neuroendocrinological, and behavioral responses in 14 patients. Ipsapirone caused hypothermia and adrenocorticotropic hormone (ACTH) release but had only minimal effects on behavior. Panic disorder patients revealed reduced hypothermic and corticoid responses to ipsapirone when compared with control subjects. Hypothermia was expected to reflect presynaptic 5-HT1A receptor activation, while corticoid responses showed activation of postsynaptic 5-HT1A receptors. McDougle *et al.* (68) undertook a placebo-controlled study to subsequently test the efficacy of buspirone in OCD patients. Buspirone was no different from the placebo as a treatment agent. Its role as an augmenting agent in specific refractory cases remains of interest. For further details, see Supplement 1.

Neuroimaging

PET Studies on Healthy Volunteers and Anxiety Disorder Patients. Several positron emission tomography studies on healthy subjects (69,70) and patients with anxiety disorders (71,72) were performed, inspired by the effects found in mice and pharmacological models, showing increased anxious behavior with lower 5-HT1A functioning. Neuroimaging data reveals that reduced 5-HT1A binding is a pathophysiological characteristic of both anxiety and depression and may represent a common neurobiological process in the development of these stress-related disorders. For details on topology of 5-HT1A binding changes and regions of interests, see Table 4.

The distribution of the 5-HT1A receptor in the human brain (Figure 1) can be quantified using radiolabeled ligands. WAY-100635 is a specific 5-HT1A receptor antagonist that binds with high affinity to the 5-HT1A receptor (16,70,73). Labeled with the [*carbonyl*-^{11}C], it can be used safely for quantitative analysis of the binding to 5-HT1A receptors (74–76).

Using [*carbonyl*-^{11}C]WAY-100635 in healthy subjects, a significant negative correlation between 5-HT1A binding potential (BP) and anxiety scores was observed, specifically in the dorsolateral prefrontal, anterior cingulate, parietal, and occipital cortices (69). These findings were consistent with results from animal studies showing increased anxiety in mice lacking 5-HT1A receptors (24). This could explain the anxiolytic effect of partial 5-HT1A receptor agonists. However, the results were not replicated by another study in male healthy subjects (70).

Panic disorder was investigated by Neumeister *et al.* (72) using the radioligand ((18)F-trans-4-Fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide) and PET. Regions of interest consisted of brain structures with high concentrations of postsynaptic 5-HT1A receptors, i.e., the anterior and posterior cingulate, anterior insular, mesiotemporal, anterior temporopolar cortices, and raphe nuclei. When patients with PD, patients with PD and comorbid depression, and healthy control subjects were compared, it was revealed that distribution volumes did not differ between the two PD groups, while both patient groups differed significantly from control subjects, showing a lower volume of distribution of the radioligand in the anterior cingulate, posterior cingulate cortices, and raphe nuclei. The abnormal function of 5-HT1A receptors appeared to impact specifically on cortical circuitries (anterior and posterior cingulate cortices) that are

Table 4. Human PET Studies of Changes in 5-TH1A Receptor Binding Associated with Anxiety Disorders

Patients/Healthy Subjects	Radiotracer	Binding Potential/Distribution Volume	References
PTSD (12/11)	[^{18}F]FCWAY	= RN, ATPC, PCG, INS, ACC, MTC	79
SAD (12/18)	[^{11}C]WAY-100635	↓ AMY, ACC, INS, RN, MOFC	71
PD (16/19)	[^{11}C]WAY-100635	↓ RN, AMY, OFC, ALTC (untreated), ↓ RN, HIP, AMTC (treated)	77
PD (16/15)	[^{18}F]FCWAY	↓ ACC, PCG, RN	72
SAD/PD (0/12)	[^{11}C]WAY-100635	↓ HIP, SGC, PCG after 12 weeks SSRI treatment	8
MDD/PD (28/0)	[^{11}C]WAY-100635	↓ TEM, ACC, INS, PHG, HIP in MDD with comorbid PD	78
Healthy Volunteers (0/19)	[^{11}C]WAY-100635	Negative correlation BP and NEO-PI-R in ACC, PAR, OCC, DLPFC	69
Healthy Volunteers (0/61)	[^{11}C]WAY-100635	No significant correlation of receptor BP with anxiety scores	70

5-TH1A, serotonin-1A; ↓, significant decrease; =, changes were not significant; ACC, anterior cingulate cortex; ALTC, anterior lateral temporal cortex; AMTC, anterior mediotemporal cortex; AMY, amygdala; ATPC, anterior temporopolar cortex; BP, blood pressure; DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; MDD, major depressive disorder; MOFC, medial orbitofrontal cortex; MTC, mesiotemporal cortex; NEO-PI-R, Revised NEO Personality Inventory; OCC, occipital cortex; OFC, orbitofrontal cortex; PAR, parietal cortex; PCG, posterior cingulate gyrus; PD, panic disorder; PET, positron emission tomography; PHG, parahippocampal gyrus; PTSD, posttraumatic stress disorder; RN, raphe nuclei; SAD, social anxiety disorder; SGC, subgenual cortex; SSRI, selective serotonin reuptake inhibitor; TEM, temporal cortex.

associated with the regulation of anxiety according to electrophysiological and functional studies in humans, nonhuman primates, and 5-HT1A receptor knockout studies in mice (25).

Nash *et al.* (77) measured 5-HT1A receptor binding in untreated patients after recovery through treatment with SSRIs. Compared with healthy control subjects, in nine PD patients binding was reduced significantly in the raphe nuclei, amygdala, orbitofrontal, and temporal cortices. Recovered patients showed reduced presynaptic binding; however, no significant reduction in postsynaptic binding was observed. This finding is consistent with predictions from studies with knockout mice.

A study on social anxiety disorder (SAD) was carried out by Lanzenberger *et al.* (71) examining the role of 5-HT1A receptor binding potential in the limbic and paralimbic system, including amygdala, hippocampus, insula, cingulate, and orbitofrontal cortices. These regions were selected because of their central role in the neural processing of fear and anxiety. Using PET and the radioligand [*carbonyl*-^{11}C]WAY-100635, a group of 12 unmedicated male SAD patients was compared with 18 healthy control subjects. The findings demonstrated a significantly lower 5-HT1A receptor binding potential in SAD patients in the hippocampus (−9.7%), insula (−28.0%), anterior cingulate cortex (−23.8%), amygdala (−21.4%), medial orbitofrontal cortex (−18.4%), and raphe nuclei (−36.4%). After a Bonferroni correction for multiple comparisons, amygdala (p = .024), insula (p = .024), and anterior cingulate cortex (p = .032) remained significant. These results underline the key role of the above brain areas in modulating anxious states.

Another interesting study by Sullivan *et al.* (78) investigated the association between anxiety scores in major depressive disorder (MDD) and regional 5-HT1A binding. Cortical 5-HT1A binding seems to play a role in the expression of different anxious behaviors occurring in MDD with different relationships to psychic as compared to somatic anxiety. Lower 5-HT1A BP in patients with comorbid PD was associated with higher somatic and lower psychic anxiety. The authors argue that a differentiation between the somatic and psychic components of anxiety may be useful in the development of new therapeutic treatments.

Although PTSD is commonly comorbid with other anxiety disorders and responds to treatment with SSRIs, patients with PTSD do not show altered 5-HT1A expression (79).

Pharmacological Effects on 5-HT1A Receptor Binding. Positron emission tomography can be used to investigate drug effects on 5-HT1A receptor binding; however, not all neuroimaging studies are in agreement about treatment effects on presynaptic or postsynaptic 5-HT1A receptor binding (80). Several studies suggested that treatment effects of SSRIs might be associated with functional or expression changes in 5-HT1A receptors. This data is in accordance with the BP reduction of 5-HT1A receptors in limbic regions. Sargent *et al.* (81) measured a statistically insignificant decrease in BP of 5-HT1A in the raphe nuclei after a 6-week treatment with paroxetine. Furthermore, a continued reduction of the 5-HT1A BP in clinically recovered depressed patients was proposed as a trait variable of depression (82). Although these results suggest that 5-HT1A receptors possess a plasticity and reactivity during chronic SSRI treatment, there is still insufficient data available to explain this phenomenon more accurately in patients. According to the transgenic mice models, lower 5-HT1A BP may increase vulnerability toward anxiety disorders. However, one may speculate that the reduction of 5-HT1A receptor binding might also be a compensatory mechanism, especially in the raphe region, within the serotonergic system. This compensatory mechanism may be insufficient in patients lacking further downregulation, therefore further lowering the 5-HT1A receptor binding by treatment may overcome this insufficient compensation. A further possible explanation is that the affinity of 5-HT1A and radioligands may change in the course of some weeks; however, this remains unobserved as only BP ($B_{max.}/K_D$) has been measured and binding of the frequently used radioligand [*carbonyl*-11C]WAY-100635 may not be identical to both the high- and low-affinity state of the 5-HT1A receptor. Furthermore, 5-HT1A data measured with [*carbonyl*-11C]WAY-100635 and based on reference models has to be confirmed by PET studies with arterial blood sampling, given the sometimes contradictory results of these methods.

A significant decrease in 5-HT1A receptor binding after treatment with escitalopram in patients suffering from anxiety disorders was recently reported by our neuroimaging group (8). After 12 weeks of treatment, we observed a significant reduction in 5-HT1A receptor binding in the hippocampus (p = .006), subgenual (p = .017), and posterior cingulate (p = .034) cortices, indicating that long-term administration may cause a decrease in the inhibitory modulation of 5-HT on GABAergic and glutaminergic neurons mediated by a reduction of 5-HT1A receptors.

Genetic Polymorphisms of the 5-HT1A Receptor

Allelic variations in 5-HT1A receptor expression seem to play an important role in the development and modulation of individual differences in anxiety-related personality traits and anxiety disorders (83,84). Results indicate that these polymorphisms also influence therapeutic responses to serotonergic agents. For further details, see Supplement 1.

Conclusions

Evidence from preclinical and clinical research, including genetic studies, pharmacological trials, and neuroimaging, reveals a substantial impact of the serotonin system and particularly the 5-HT1A receptor on the neurobiology of anxiety. However, the serotonin system affects and is influenced by many other neurotransmitters in brain structures essential for the processing and expression of anxiety (85). Animal studies showed modulatory effects of the 5-HT1A receptor on glutamatergic, GABAergic, and dopaminergic neurons, especially in the (pre)frontal cortex and limbic areas (86–89). There is a lack of human studies investigating the effects of 5-HT1A receptor activation on other neurotransmitter systems. Future pharmacological functional magnetic resonance imaging (fMRI) studies with 5-HT1A agonists or antagonists will mainly show the effects on the glutamatergic and GABAergic system. However, it must be stressed that for a more comprehensive model supporting the role of the 5-HT1A receptor in anxiety disorders, it will be necessary to include data on other neurotransmitters. As most of the above-mentioned studies draw their conclusions based on animal models, it is necessary to note that it is generally difficult to make inferences on the pathogenesis in humans from preclinical results. Firstly, the periods of increased brain plasticity are clearly different in humans compared to rodents. There are also inherent problems in reproducing the typical stressful experiences of humans in animal tests. Therefore, direct methodological and interspecies comparisons have their limitations. Systematic multimodal studies in primates are necessary to link the findings of 5-HT1A transgenic mice with clinical data more convincingly. Given the lack of knockout models in primates, the effects of 5-HT1A receptor agonists and antagonists should be studied in different developmental periods and may then be

combined with quantifications of 5-HT1A receptor binding, using nondisplaceable radioligands and longitudinal molecular neuroimaging. By combining these approaches with the investigations of genetic polymorphisms in the serotonergic system and environmental risk factors, such as stress, a causal model of the influence of 5-HT1A in the etiology of anxiety disorders may be found in primates. It can be stated that anxiety disorders are biologically heterogeneous conditions influenced by genetic, epigenetic, and environmental factors. Therefore, dysregulation of 5-HT1A receptors cannot be considered as the one simple primary factor in anxiety disorders. Possibly, the role of the serotonin system in anxiety disorders is adaptive rather than pathogenic. In the future, a better understanding of 5-HT1A receptor function will provide insight into the origins and improved clinical management of anxiety disorders.

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Supplementary material cited in this article is available online.

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