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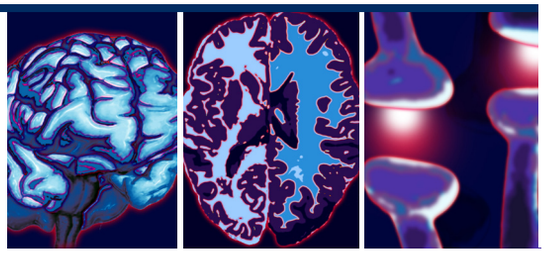

Biased agonism at serotonin 5-HT_{1A} receptors: preferential postsynaptic activity for improved therapy of CNS disorders

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Practice points

- Serotonin or 5-hydroxytryptamine (5-HT)$_{1A}$ receptors are attractive targets for pharmacotherapy of pathologies associated with dysfunctional serotonergic neurotransmission, including anxiety, depression, Parkinson's disease, pain and schizophrenia.
- 5-HT_{1A} receptors are expressed both as presynaptic autoreceptors on serotonergic cell bodies in the raphe and as postsynaptic heteroreceptors in multiple brain regions including the cortex, hippocampus, septum and hypothalamus.
- The signaling cascades elicited by 5-HT_{1A} receptor activation differ between brain regions: different G-protein subtypes, different second messengers and different neurochemical read-outs.
- The concept of 'biased agonism' or 'functional selectivity' asserts that agonists can preferentially direct receptor signaling to specific intracellular responses. This opens the possibility of targeting receptors in specific cellular environments or brain regions.
- F15599 is a selective 5-HT_{1A} receptor agonist that exhibits biased agonism, preferentially activating Gαi versus Gαo G-protein subtypes. F15599 preferentially activates ERK1/2 phosphorylation more than G-protein, receptor internalization or adenylyl cyclase inhibition.
- F15599 stimulates rat medial prefrontal cortex pyramidal neuron electrical activity and dopamine release (controlled by postsynaptic 5-HT_{1A} receptors) at low doses that do not inhibit raphe serotonergic neuron electrical activity or hippocampal 5-HT release (controlled by presynaptic 5-HT_{1A} receptors).
- F15599 preferentially stimulates c-Fos expression and ERK1/2 phosphorylation in rat prefrontal cortex, with less pronounced effects in the raphe. This preferential postsynaptic activity is not observed with other 5-HT_{1A} agonists.
- In rats F15599 exhibits potent antidepressant-like activity in the forced swim test, inhibits stress-induced ultrasonic vocalization and attenuates phencyclidine-induced cognitive impairments in reversal learning, in novel object recognition and in a hole-board test.
- At 'antidepressant' doses in rats, F15599 does not induce serotonin syndrome, does not disrupt attentional performance, does not impair working memory and does not inhibit prepulse inhibition of startle response.

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SUMMARY Serotonin or 5-hydroxytryptamine (5-HT)$_{1A}$ receptors are widely expressed in the brain and have extensive influence in the control of mood, cognition, movement and pain. In order to achieve optimal therapeutic benefit from targeting these receptors, 'biased agonists' (also known as 'functionally selective agonists') are desirable in order to preferentially activate receptor subpopulations in brain regions that mediate therapeutic activity, whilst avoiding those that control other effects. For example, clinical studies indicate that antidepressant activity is favored when 5-HT$_{1A}$ autoreceptor activation is minimized and postsynaptic 5-HT$_{1A}$ receptor activation is reinforced. F15599 is a novel biased agonist that exhibits a distinctive signal transduction 'fingerprint' *in vitro* and preferential postsynaptic activation of cortical 5-HT$_{1A}$ receptors *in vivo*. This profile confers on F15599 a superior activity in animal models of depression and cognition, with a wide therapeutic margin relative to side effects. The use of biased agonists at 5-HT$_{1A}$ receptors constitutes an attractive strategy to manage CNS disorders arising from dysfunctional serotonergic neurotransmission.

Since the identification of serotonin (5-hydroxytryptamine [5-HT]) as a CNS neurotransmitter in 1954 [1–3], extensive investigation has been devoted to its complex functions. Indeed, 5-HT interacts with 13 receptor subtypes, divided into seven families (5-HT$_1$ to 5-HT$_7$) based on amino acid sequence and functional homologies [4]. In addition, functionally distinct splice variants occur in 5-HT$_4$ and 5-HT$_7$ receptors [5], and 5-HT$_{2C}$ receptors undergo RNA editing that modifies the receptor's amino acid sequence and its constitutive activity [6]. 5-HT$_{1A}$ receptors have attracted particular interest because they exert inhibitory influence on serotonergic tone, are widely distributed in postsynaptic brain regions, such as the cortex, septum and hippocampus, and are implicated in the control of mood, cognition and pain [7–10].

Accordingly, 5-HT$_{1A}$ receptors are targets for pharmacotherapy of a variety of CNS disorders **(Table 1)**. For example, the partial agonists buspirone and tandospirone are clinically employed anxiolytics [8,11]. The antidepressant effects of 5-HT$_{1A}$ receptor agonists [12–14] have been explored with flesinoxan [15,16] and with flibanserin, which also counters female sexual dysfunction [17,18]. 5-HT$_{1A}$ receptor agonism is also a prominent feature of several anti-Parkinson's disease drugs, including bromocriptine, lisuride and pardoprunox (SLV308) [19–21]. 5-HT$_{1A}$ receptor activation plays an important role in the action of atypical antipsychotics [22,23]. Indeed, clozapine, ziprasidone, aripiprazole and lurasidone act as 5-HT$_{1A}$ receptor partial agonists, as well as possessing other pharmacological properties [24–26]. 5-HT$_{1A}$ receptor agonists such as xaliproden and repinotan (BAYx3702) have been tested for potential neuroprotective activity [27–30] and the potent and high-efficacy agonist, befiradol, is active in a range of chronic pain models [9,31].

However, current drugs acting as 5-HT$_{1A}$ agonists may be suboptimal in their profile of activity, because they indiscriminately activate 5-HT$_{1A}$ receptors in those brain regions that are responsible for therapeutic actions and also in those regions that mediate other responses, which include side effects. For example, whereas activation of postsynaptic 5-HT$_{1A}$ receptors is thought to mediate antidepressant properties, activation of raphe-located 5-HT$_{1A}$ autoreceptors is implicated in a delay of onset of antidepressant efficacy (see discussion later) [32–34]. Hypothalamic 5-HT$_{1A}$ receptors are involved in thermoregulation and neuroendocrine control, whereas septum/hippocampal receptors control acetylcholine release and aspects of memory function [1,10,35], thus activation of these receptor subpopulations can elicit hormonal and cognitive side effects. Therefore, it would be desirable to identify agonists that preferentially target those 5-HT$_{1A}$ receptors that are implicated in therapeutic properties whilst avoiding interactions at other 5-HT$_{1A}$ receptor subpopulations: such a 'biased agonist' could exhibit a wider therapeutic margin between beneficial effects and side effects **(Figure 1)**. The present article summarizes evidence that 5-HT$_{1A}$ receptors in different brain regions exhibit distinct molecular signaling properties, thus providing a mechanistic basis for preferential targeting of receptor subpopulations using pharmacological agents, such as the novel agonist F15599.

Differential functions of pre- & post-synaptic 5-HT$_{1A}$ receptors

5-hydroxytryptamine$_{1A}$ receptors elicit differential, and sometimes opposing, responses in different brain regions. Receptor inactivation studies using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline demonstrated the existence of a 5-HT$_{1A}$ receptor reserve in the raphe for inhibition

Table 1. Examples of clinically tested drugs with 5-hydroxytryptamine$_{1A}$ receptor properties.

Indication	Compound	Trade name or highest development	Company	Mechanism of action	Ref.
Mood disorders					
Anxiety (GAD)	Buspirone	Buspar®	Bristol-Myers Squibb	5-HT$_{1A}$ partial agonist	[8]
Anxiety (GAD)	Tandospirone	Sediel®	Dainippon Sumitomo	5-HT$_{1A}$ partial agonist	[105]
Anxiety (GAD)	Osemozotan	Phase II	MediciNova/Mitsubishi	5-HT$_{1A}$ partial agonist	[94]
Depression	Vilazodone	Viibryd®	Forest/Merck KGa	SRI, 5-HT$_{1A}$ partial agonist	[72]
Depression	Lu-AA21004	Phase III	Lundbeck/Takeda	SRI, 5-HT$_{1A}$ partial agonist	[74]
Depression, FSD	Flibanserin	Phase III (d)	Boehringer Ingelheim	5-HT$_{1A}$ agonist, 5-HT$_{2A}$ antagonist, D$_4$ partial agonist	[18]
Depression	F15599	Phase I (d)	Pierre Fabre	Selective 5-HT$_{1A}$ agonist	[99]
Depression (as adjunct therapy)	Pindolol	Visken®	Novartis	5-HT$_{1A}$ partial agonist, adrenergic β-blocker	[32]
Schizophrenia					
Schizophrenia	Clozapine	Clozaril®	Novartis	Multireceptor, 5-HT$_{1A}$ partial agonist	[23]
Schizophrenia	Ziprasidone	Geodon®	Pfizer	Multireceptor, 5-HT$_{1A}$ partial agonist	[23]
Schizophrenia	Aripiprazole	Abilify®	Otsuka/Bristol-Myers Squibb	Multireceptor, D$_2$ and 5-HT$_{1A}$ partial agonist	[26]
Schizophrenia	Lurasidone	Latudar®	Dainippon Sumitomo	Multireceptor, 5-HT$_{1A}$ partial agonist	[25]
Schizophrenia	Cariprazine	Phase III	Gedeon Richter/Forest	D$_3$/D$_2$ and 5-HT$_{1A}$ partial agonist, 5-HT$_{2B}$ antagonist	[130]
Schizophrenia	Bifeprunox	Phase III (d)	Solvay	D$_2$ and 5-HT$_{1A}$ partial agonist	[131]
Pain					
Migraine	Naratriptan	Naramig®	GlaxoSmithKline	5-HT$_{1B}$ agonist, 5-HT$_{1A}$ agonist	[132]
Neuropathic	Befiradol	Phase II	Pierre Fabre	Selective 5-HT$_{1A}$ agonist	[9]
Neurodegenerative disorders					
Alzheimer's disease	Lecozotan	Phase III	Wyeth	5-HT$_{1A}$ antagonist	[133]
Parkinson's disease	Bromocriptine	Parlodel®	Novartis	D$_2$ and 5-HT$_{1A}$ partial agonist	[19]
Parkinson's disease	Lisuride	Dopergin®	Bayer	D$_2$ partial agonist, 5-HT$_{1A}$ agonist, 5-HT$_2$ antagonist	[19]
Parkinson's disease	Pardoprunox	Phase III	Solvay	5-HT$_{1A}$ agonist, D$_2$ partial agonist	[21]
Ischemic stroke	Piclozotan	Phase III	Daiichi Asubio	5-HT$_{1A}$ partial agonist	[134]
Ischemic stroke	Repinotan	Phase II (d)	Bayer	Selective 5-HT$_{1A}$ agonist	[27]
Peripheral neuropathy, ALS	Xaliproden	Phase III (d)	Sanofi-Aventis	5-HT$_{1A}$ partial agonist	[29]

5-HT: 5-hydroxytryptamine; ALS: Amyotrophic lateral sclerosis; d: Development discontinued; FSD: Female sexual dysfunction; GAD: Generalized anxiety disorder; SRI: Serotonin reuptake inhibitor.

of 5-HT synthesis [36]. By contrast, a receptor reserve was not observed in the hippocampus for inhibition of adenylyl cyclase activity or for control of hypothermia [37,38]. The agonist radiotracer [^{3}H]8-OH-DPAT showed a fivefold higher affinity in the hippocampus than in raphe membranes [39], suggesting that the receptor–G-protein coupling state of the receptor differs between the two brain regions. Furthermore, although 5-HT$_{1A}$ receptors are coupled to inhibition of adenylyl cyclase in the hippocampus, they are not coupled to this response in the raphe homogenates [40]. By contrast, 5-HT$_{1A}$ receptor-mediated inhibition of inositol phosphate synthesis by 8-OH-DPAT and flesinoxan was observed in the raphe but not in the hippocampus [39]. An immuno-precipitation study found that, in raphe, 5-HT$_{1A}$ receptors preferentially couple to Gαi3 subtypes whereas they couple preferentially to Gαo in the hippocampus and to a combination of G-proteins in the cortex

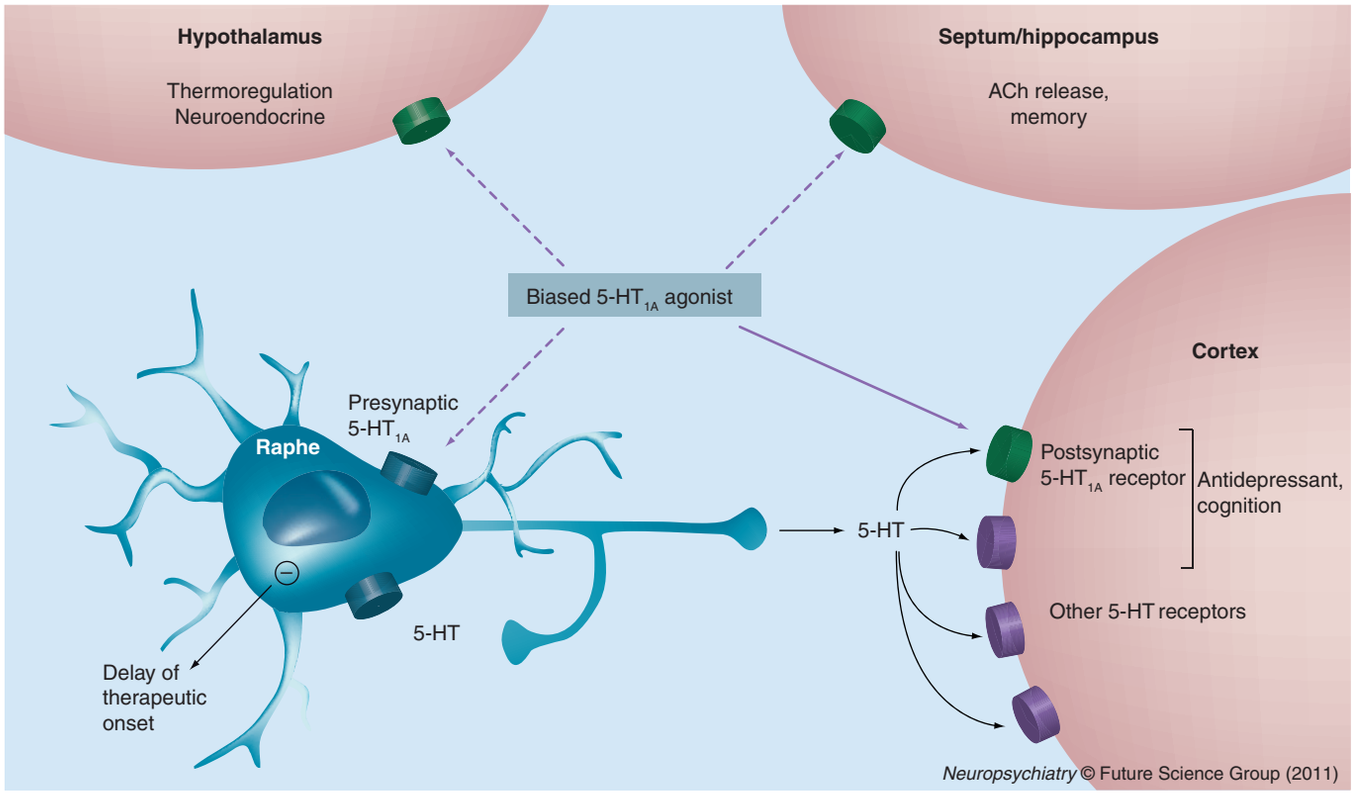

Figure 1. Concept of a biased agonist with preferential activity at postsynaptic cortical 5-hydroxytryptamine$_{1A}$ receptors. Activation of postsynaptic 5-HT$_{1A}$ receptors mediates therapeutic (e.g., antidepressant) properties, whereas activation of raphe autoreceptors is implicated in delay of therapeutic onset of antidepressants. Hypothalamic 5-HT$_{1A}$ receptors are involved in thermoregulation and neuroendocrine control whereas septum/hippocampal receptors control ACh release and aspects of memory function. A biased agonist preferentially targeting cortical 5-HT$_{1A}$ receptors could exhibit a wider margin between therapeutic effects and side effects.
5-HT: 5-hydroxytryptamine; ACh: Acetylcholine.

and hypothalamus [41]. 5-HT$_{1A}$ receptor agonists also increased ERK1/2 phosphorylation in the cortex, presumably by direct activation of postsynaptic 5-HT$_{1A}$ receptors. By contrast, 5-HT$_{1A}$ receptor agonists inhibited ERK1/2 phosphorylation in the hippocampus, likely via an inhibition of 5-HT release caused by activation of presynaptic 5-HT$_{1A}$ receptors [42–44].

At a neurochemical level, activation of presynaptic 5-HT$_{1A}$ receptors expressed on serotonergic neurons elicits inhibition of 5-HT release in terminal regions such as the hippocampus and cortex. By contrast, activation of postsynaptic cortical 5-HT$_{1A}$ heteroreceptors expressed on glutamatergic pyramidal cells and/or GABAergic interneurons elicited increased dopamine release [45–47]. In rodent behavioral tests, anxiolytic activity is mediated by activation of presynaptic 5-HT$_{1A}$ receptors [8,12], whereas antidepressant-like activity is mediated by activation of postsynaptic receptors [12]. Accordingly, mice that were genetically manipulated to increase raphe 5-HT$_{1A}$ receptor expression exhibited depressive-like behavior and were resistant to antidepressant treatment [48]. These observations are consistent with clinical observations in depressed patients treated with serotonin reuptake inhibitors (SRIs): desensitization of presynaptic 5-HT$_{1A}$ receptors is necessary before antidepressant efficacy is achieved [32,34]. Indeed, the therapeutic onset of SRIs was accelerated when 5-HT$_{1A}$ autoreceptors were antagonized with pindolol. This 5-HT$_{1A}$ receptor partial agonist (and β-adrenergic antagonist) competes with 5-HT at 5-HT$_{1A}$ autoreceptors and thus mimics the desensitization of this receptor subpopulation [32]. Other studies with pindolol provided support for the importance of postsynaptic 5-HT$_{1A}$ receptor activation in antidepressant action. Indeed, when feedback inhibition of presynaptic 5-HT$_{1A}$ receptors was blocked with pindolol, the anxiolytic, buspirone

(which is not effective as a monotherapy against depression) exerted clinical antidepressant influence, presumably through activation of postsynaptic 5-HT$_{1A}$ receptors [49]. In cognition tests, 8-OH-DPAT facilitated rat passive avoidance at low doses, whereas higher doses impaired performance [50,51]. This is likely owing to differential effects at pre- and post-synaptic 5-HT$_{1A}$ receptors, respectively [10]. Indeed, microinjection of the 5-HT$_{1A}$ receptor weak partial agonist, S15535, into the hippocampus reversed the memory deficit elicited by systemic injection of 8-OH-DPAT in a spatial discrimination task [35], indicating that activation of postsynaptic receptors in this brain region was detrimental to mnesic performance. Finally, activation of presynaptic 5-HT$_{1A}$ receptors may facilitate addiction-related behaviors, whereas activation of postsynaptic 5-HT$_{1A}$ receptors inhibits them [52].

It should be noted that the diverse effects of pre- and post-synaptic 5-HT$_{1A}$ receptor activation are not caused by the presence of receptor subtypes. Indeed, only a single 5-HT$_{1A}$ receptor gene has been identified in humans and rats: it has no introns or splice variants [53,54] and thus the variety of responses described earlier are attributable to regional differences in G-protein subtypes [41], regulators of G-protein signaling [55] or transcriptional regulation. Indeed, the expression of 5-HT$_{1A}$ receptors is differentially regulated by a single nucleotide polymorphism in the promoter region of the 5-HT$_{1A}$ receptor gene (*rs6295*; C[-1019]G substitution) [56,57]. This single nucleotide polymorphism impairs repression of the 5-HT$_{1A}$ promoter by the NUDR/DEAF-1 transcription factors in raphe cells, consistent with overexpression of presynaptic 5-HT$_{1A}$ receptors [17,58]. Thus, the *rs6295* polymorphism is associated with higher levels of remission failure and suicidal behavior in depressed patients, consistent with impaired antidepressant efficacy owing to excessive feedback inhibition by presynaptic 5-HT$_{1A}$ receptors. Furthermore, schizophrenia patients expressing the *rs6295* polymorphism exhibit deficient cognitive performance [59] and impaired negative symptoms and cognitive response to antipsychotics [60–63]. These observations are likely related to the fact that the *rs6295* polymorphism also causes hypofunction of 5-HT$_{1A}$ receptors in the cortex [56,64,65], thus resulting in an overall imbalance of pre- versus postsynaptic receptor function. Some other 5-HT$_{1A}$ receptor single nucleotide polymorphisms are also associated with depressive traits and antidepressant treatment response [66,67], reinforcing the assertion that an imbalance of 5-HT$_{1A}$ receptor function is deeply implicated in mood disorders.

Taken together, the aforementioned observations indicate that indiscriminate activation of all 5-HT$_{1A}$ receptor subpopulations is unlikely to provide optimal therapeutic benefit. Accordingly, efforts have been made to preferentially influence 5-HT$_{1A}$ receptor subpopulations. For example, SB-649915-B is a drug that combines SRI and 5-HT$_{1A}$ antagonist properties [68,69], aiming to avoid feedback inhibition of 5-HT release by blocking the activation of 5-HT$_{1A}$ autoreceptors [32,70]. However, whilst antidepressant efficacy may be enhanced by 5-HT$_{1A}$ autoreceptor antagonism, it may also be hindered by antagonism of postsynaptic 5-HT$_{1A}$ receptors [12,71]. Vilazodone, Lu-AA21004 and VN2222 exemplify another approach: they act as SRIs whilst retaining partial agonist activity at 5-HT$_{1A}$ receptors [72–74]. Indeed, pindolol is a partial agonist at 5-HT$_{1A}$ receptors, as discussed above [32,75]. However, a partial agonist strategy is not without uncertainty: is the agonism sufficiently modest to ensure antagonism of 5-HT$_{1A}$ autoreceptors? Is the agonism sufficiently prominent to avoid blocking postsynaptic 5-HT$_{1A}$ receptors? Such considerations suggest that it would be desirable to select compounds that preferentially interact with 5-HT$_{1A}$ receptor subpopulations mediating therapeutic properties (e.g., cortical postsynaptic sites), whilst minimizing interactions with other 5-HT$_{1A}$ receptor subpopulations.

Biased agonism: differential activation of 5-HT$_{1A}$ receptor signaling

Much attention has recently been given to the idea of 'biased agonism' (also known as 'functional selectivity' or 'agonist-directed signaling') [76–79]. According to this concept, agonists may preferentially direct receptor signaling to one G-protein or second messenger response whilst not affecting, or even blocking, another response **(Figure 2)**. If the different signaling responses mediate distinct functional effects (e.g., therapeutic vs side effects), then biased agonism offers a strategy to identify more effective and better-tolerated drugs. Examples of serotonergic 'biased agonism' have been reported at 5-HT$_2$ receptors *in vitro* and *in vivo* and may underlie propsychotic effects of some CNS agents [80–82].

In the case of 5-HT$_{1A}$ receptors, several pharmacological studies show that agonists

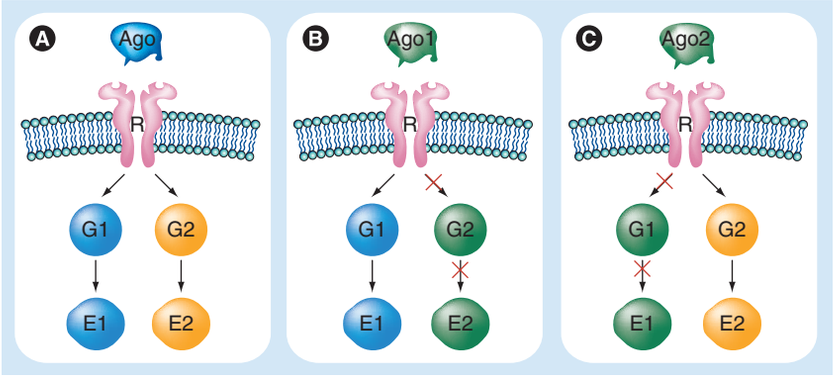

Figure 2. Concept of biased agonism (also known as 'functional selectivity'). The concept of 'biased agonism' **(B & C)** postulates that different agonists (Ago1 or Ago2) acting at the same receptor may be capable of preferentially activating different signal transduction responses, such as G-protein subtypes and coupled effectors (G1/E1 or G2/E2) [76,77], whereas the concept of 'intrinsic activity' **(A)** postulates that agonists will activate all signaling pathways available to the receptor. Ago: Agonist; E: Effector; G: G-protein; R: Receptor.

can differentially activate signaling responses *in vitro*. In electrophysiological experiments on *Xenopus* oocytes transiently expressing 5-HT_{1A} receptors, the agonists, 5-HT, L694247 and F13714, stimulated G-protein-activated inwardly rectifying K^+ currents with similar efficacy [83]. By contrast, L694247 was more efficacious than 5-HT in the stimulation of a G-protein-independent smooth inward current, whereas F13714 acted as an antagonist for this response, as did the selective 5-HT_{1A} receptor antagonist WAY100635 [83].

A study examining G-protein subtype activation in a cloned cell line [84], found that different agonists displayed a varying balance of activation of Gαi2 and Gαi3. Rauwolscine displayed similar EC_{50} values for activation of the two G-protein subtypes, but ipsapirone showed a nearly fourfold lower EC_{50} for Gαi3 activation. 5-HT and 8-OH-DPAT had intermediate EC_{50} ratios [84]. These data indicate that 5-HT_{1A} receptor agonists can be distinguished by their relative capacity to activate different G-protein subtypes.

Another study found that the G-protein activation elicited by 5-HT via 5-HT_{1A} receptors in a Chinese hamster ovary cell line was partly blocked by preincubation with anti-Gαi3 antibodies, indicating that other G-protein subtypes also couple to 5-HT_{1A} receptors in this cell line [85]. However, in the case of the partial agonist, pindolol, preincubation with anti-Gαi3 antibodies almost completely suppressed G-protein activation. This suggested that pindolol preferentially elicited 5-HT_{1A} receptor coupling to Gαi3 and not to other G-protein subtypes, a mechanism that may underlie pindolol's capacity to preferentially interact with 5-HT_{1A} receptors in the raphe, as observed in PET studies [86,87]. Drug differences were also seen in rat raphe transduction: buspirone elicited 5-HT_{1A} receptor coupling to Gαi2, Gαi3 and Gαo and inhibition of adenylyl cyclase [88]. By contrast, $^+$8-OH-DPAT only elicited coupling to Gαi3 and did not elicit the other responses.

Among the drugs that have been clinically tested, flibanserin reportedly activates postsynaptic 5-HT_{1A} receptors in the human cortex and hippocampus more than presynaptic sites in the raphe [18,89,90], although interpretation of these data is complicated by variations in the route of administration and interactions with 5-HT_{2A} and D_4 receptors [90,91]. The antipsychotic aripiprazole, which reportedly shows biased agonism at D_2 receptors [92], stimulated postsynaptic 5-HT_{1A} receptors controlling frontal cortex dopamine release at doses tenfold lower than those that inhibit 5-HT release by activation of presynaptic 5-HT_{1A} receptors, suggesting a postsynaptic preference [93]. By contrast, 8-OH-DPAT activated presynaptic 5-HT_{1A} receptors at lower doses than those that activate postsynaptic 5-HT_{1A} receptors in the frontal cortex [94].

Whilst the aforementioned evidence is somewhat fragmentary, it suggests that some existing 5-HT_{1A} receptor ligands may act as biased agonists with disparate influence on receptor signaling in different brain regions. Hence, the identification of novel ligands that preferentially target brain regions of interest appears pharmacologically possible and may be therapeutically advantageous.

Distinct pharmacological targeting of pre- & post-synaptic 5-HT_{1A} receptors

F15599 is a potent, selective and high efficacy agonist of 5-HT_{1A} receptors. Chemically related compounds include befiradol (F13640) and F13714 [95–97], but not 8-OH-DPAT or buspirone **(Figure 3)**. Detailed comparison of F15599 and F13714 shows that they differ markedly in their *in vitro* signaling profiles and in their *in vivo* properties at subpopulations of 5-HT_{1A} receptors. Therefore, although F15599, F13714, 8-OH-DPAT and 5-HT all behaved as efficacious agonists in cellular tests of G-protein activation, adenylyl cyclase inhibition, ERK1/2 phosphorylation and receptor internalization,

the order of potency for stimulation of these responses was specific to each agonist **(Table 2)**. Thus, F15599 showed marked potency for ERK1/2 phosphorylation (EC_{50} ~15 nM) but lower potency for other responses (EC_{50} 100–350 nM), whereas 5-HT preferentially elicited adenylyl cyclase inhibition [98]. Each agonist exhibited its own 'signaling fingerprint', possibly because of agonist-directed coupling of 5-HT$_{1A}$ receptors to different G-protein subtypes. Indeed, 5-HT activated both Gαi and Gαo over a similar concentration range, whereas F15599 activated Gαi more potently and more efficaciously than Gαo. F13714 and 8-OH-DPAT exhibited intermediate profiles [98]. Given that 5-HT$_{1A}$ receptors couple to different G-protein subtypes depending on the brain area [41], this suggests that biased agonists can, *de facto*, preferentially target certain brain regions and functional responses.

However, caution is desirable when extrapolating from *in vitro* effects to *in vivo* functional responses because cross-talk may render receptor-level biased agonism redundant in more integrated systems [34,78]. In the case of F15599, a series of studies [98–102] have demonstrated that its distinctive 'signaling fingerprint' translates to a distinctive preferential activation of postsynaptic (mainly cortical) 5-HT$_{1A}$ receptors, with less influence on presynaptic 5-HT$_{1A}$ receptors. By contrast, F13714 exhibits an opposite preference, with more pronounced activation of 5-HT$_{1A}$ autoreceptors and less potent activity at cortical receptors.

Firstly, in rat electrophysiological tests, F15599 stimulated frontal cortex pyramidal cell electrical activity at low doses (minimal effective dose 0.2 µg/kg intravenously), whereas a much higher dose was necessary to inhibit raphe neuron firing (minimal effective dose 8.2 µg/kg

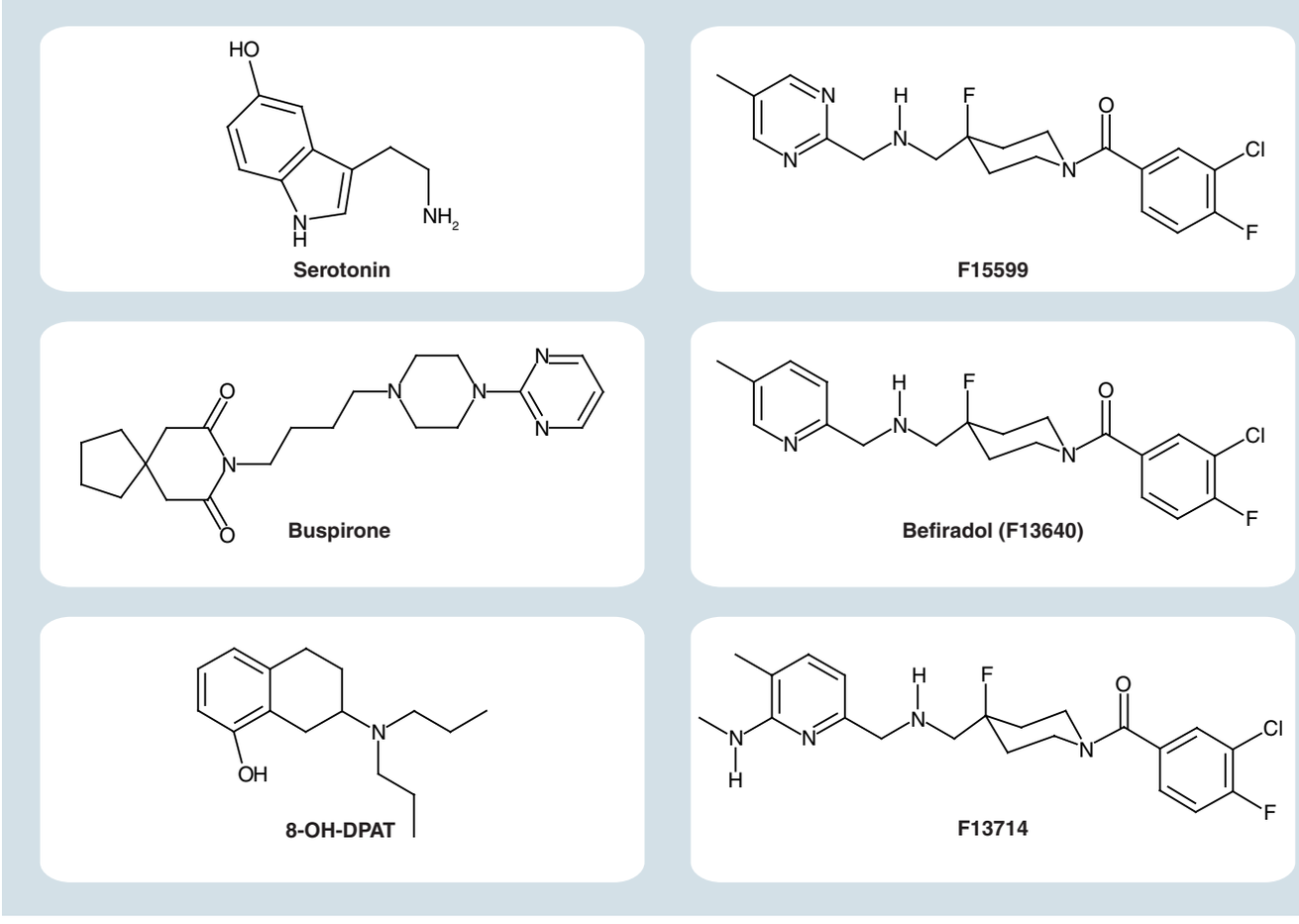

Figure 3. 5-hydroxytryptamine$_{1A}$ receptor agonists. F15599 and its chemical congeners, befiradol and F13714, are highly efficacious and selective 5-hydroxytryptamine$_{1A}$ receptor agonists [95,97]. They are chemically distinct from serotonin, buspirone and 8-OH-DPAT.

Table 2. Rank order of potency for activation of cloned human 5-hydroxytryptamine$_{1A}$ receptor signaling in cell lines.

Agonist	First response		Second response		Third response		Fourth response
F15599	pERK	>>	G-protein	>	Internalization	>	cAMP
F13714	pERK	>	Internalization	=	G-protein	≥	cAMP
(+)8-OH-DPAT	pERK	>>	cAMP	>	Internalization	≥	G-protein
Serotonin	cAMP	>	G-protein	>	pERK	>	Internalization

= Similar potency; > Greater potency; >> Much greater potency.
Data taken from [98].

intravenously) [102]. Both of these effects were antagonized by WAY100635. The electrophysiological profile of F15599 is not shared by other 5-HT$_{1A}$ agonists, such as 8-OH-DPAT, befiradol or repinotan [Lladó-Pelfort L, Assié M-B, Newman-Tancredi A, Artigas F, Celada P, Unpublished Data] [73,103,104].

Secondly, in microdialysis studies, F15599 stimulated dopamine release in rat medial prefrontal cortex at low doses (ED$_{50}$ 0.03 mg/kg intraperitoneally). This effect was associated with beneficial properties on mood and cognitive parameters and was reversed by WAY100635 [102,103,105]. By contrast, F15599 inhibited hippocampal 5-HT release at doses that were about an order of magnitude higher (ED$_{50}$ 0.24 mg/kg intraperitoneally) [102], indicating that F15599 only modestly activates 5-HT$_{1A}$ autoreceptors. This profile of activity is not shared by other 5-HT$_{1A}$ agonists, even closely related analogs, such as F13714 or befiradol [Lladó-Pelfort L, Assié M-B, Newman-Tancredi A, Artigas F, Celada P, Unpublished Data] [45,106], suggesting that the chemical structure of F15599 underlies its distinctive profile. In other experiments, where 5-HT$_{1A}$ receptor agonists were chronically administered in rats by osmotic mini-pumps, a low dose of F13714 (2.5 mg/kg/day for 3 days) was sufficient to rapidly desensitize presynaptic 5-HT$_{1A}$ receptors [107,108]. Indeed, administration of buspirone failed to elicit a decrease in hippocampal 5-HT release, indicating that 5-HT$_{1A}$ autoreceptors were no longer responsive. By contrast, F15599 did not desensitize presynaptic 5-HT$_{1A}$ receptors, except at very high doses (20 mg/kg/day for 14 days), indicating that it has little effect on somatodendritic 5-HT$_{1A}$ sites.

Thirdly, a preferential postsynaptic action of F15599 is supported by rat *ex vivo* studies of expression of the immediate early gene, *c-Fos*, in different brain regions, as determined by quantitative PCR. *c-Fos* expression provides a marker of neuronal activation state and, in the case of F15599, was markedly stimulated in the frontal cortex, but very little or not at all in the median or dorsal raphe [98]. By contrast, F13714 showed an opposite profile, strongly stimulating *c-Fos* expression in dorsal raphe, to an extent that exceeded that in the frontal cortex [109].

Fourthly, *ex vivo* studies of ERK1/2 phosphorylation in different brain regions, determined by quantitative ELISA assay, demonstrated that F15599 increased ERK1/2 phosphorylation in the rat frontal cortex (a response controlled by postsynaptic 5-HT$_{1A}$ receptors) and inhibited it in the hippocampus (a response controlled by presynaptic receptors) at similar doses [98]. By contrast, F13714 and befiradol were markedly more potent for stimulation of ERK1/2 phosphorylation in the hippocampus, indicating a preferential presynaptic action [43]. These data suggest that pronounced ERK1/2 phosphorylation may underlie the preferential cortical activity of F15599, an interpretation that is consistent with the compound's potent activation of ERK1/2 phosphorylation in cellular tests *in vitro*, as discussed earlier [98].

Fifthly, in a rat drug discrimination study, F15599 generalized to an 8-OH-DPAT cue only when high doses were administered, whereas F13714 did so at very low doses, suggesting that the cue is related to presynaptic 5-HT$_{1A}$ receptor activation [110].

Effects of preferential postsynaptic 5-HT$_{1A}$ receptor activation in models of mood & cognition

The biased agonism of F15599 at postsynaptic cortical 5-HT$_{1A}$ receptors translates to a superior behavioral profile in models of mood and cognition. Thus, F15599 potently and completely reversed immobility in the rat forced swim test (FST), a classical model of antidepressant-like activity, and inhibited shock-induced ultrasonic vocalization in rats, a measure of antistress/anxiolytic activity [99,111]. Notably, the potency of

F15599 in both these tests is as great as that of its congener, F13714, despite the fact that the latter has an over 30-fold higher affinity in *in vitro* binding experiments (0.01 nM for F13714 vs 3.4 nM for F15599) **(Table 3)** [98]. The marked *in vivo* potency of F15599 suggests that preferential activation of cortical 5-HT$_{1A}$ receptors produces accentuated effects on mood parameters.

Table 3. Comparative pharmacological profile of the postsynaptic preferential 5-hydroxytryptamine$_{1A}$ agonist, F15599, and the presynaptic preferential agonist, F13714.

	F15599	F13714	Ref.
Receptor binding and signaling			
In vitro 5-HT$_{1A}$ receptor affinity (Ki)	3.4 nM	0.01 nM	[98]
In vitro signaling potency – see **Table 2** (EC$_{50}$)	10–300 nM	~1 nM	[98]
In vitro Gαi activation (EC$_{50}$; E$_{max}$)	110 nM; 122%	0.7 nM; 110%	[98]
In vitro Gαo activation (EC$_{50}$; E$_{max}$)	850 nM; 103%	0.8 nM; 83%	[98]
In vivo 5-HT$_{1A}$ binding, mouse cortex (ID$_{50}$, ip.)	2.5	1.0	[98]
Ex vivo c-Fos frontal cortex (MED, ip.)	0.16	0.16	[98,109]
Ex vivo c-Fos dorsal raphe (MED, ip.)	No stimulation	0.16	[98,109]
Ex vivo ERK1/2 frontal cortex stimulation (MED, ip.)	0.63	0.16	[98,109]
Ex vivo ERK1/2 hippocampus inhibition (MED, ip.)	0.63	0.04	[98,109]
Electrophysiology and neurochemistry			
Electrophysiology: cortex pyramidal neurons (MED, intravenous)	0.2 µg/kg	n.t.	[102]
Electrophysiology: DRN 5-HT neurons (MED, intravenous)	8.2 µg/kg	n.t.	[102]
Microdialysis: frontal cortex dopamine (ED$_{50}$, ip.)	0.03	0.16	[102]
Microdialysis: hippocampal 5-HT (ED$_{50}$, ip.)	0.24	0.04	[102]
Microdialysis: 5-HT$_{1A}$ autoreceptor desensitization	20 mg/kg/day, 14 days	2.5 mg/kg/day, 3 days	[107,108]
Antidepressant and pro-cog. properties			
Forced swim test: systemic (ED$_{50}$, p.o.)	0.12	0.06	[99]
Ultrasonic vocalization (ED$_{50}$, ip.)	0.06	0.02	[99]
Hole-board: working memory vs PCP (dose ip.)	Pro-cog., 0.16	Inactive, 0.04	[100]
Reversal-learning flexibility vs PCP (dose ip.)	Pro-cog., 0.16	Deficit, 0.04	[100]
Novel object recognition vs PCP (dose ip.)	Pro-cog., 0.16	n.t.	[Horiguchi M, Meltzer HY, Unpublished Data]
Side effects			
Forepaw treading (ED$_{50}$, p.o.)	3.7	0.70	[99]
Flat body posture (ED$_{50}$, p.o.)	7.2	0.84	[99]
Corticosterone release (ED$_{50}$, p.o.)	0.45	0.05	[99]
Prepulse inhibition deficit (MED, ip.)	0.63	0.04	[100,135]
DNMTP working memory deficit	>0.32	0.04	[100]
5CSRTT attentional deficit (MED, ip.)	0.63	0.04	[100]

Unless stated, all *ex vivo* and *in vivo* tests were carried out in rats and doses are expressed as mg/kg.

5CSRTT: 5-choice serial reaction time test; 5-HT: 5-hydroxytryptamine; DNMTP: Delayed non-matching to position; DRN: Dorsal raphe nucleus; ip.: Intraperitoneally; MED: Minimal effective dose; n.t.: Not tested; PCP: Phencyclidine; p.o.: *Per orem*; Pro-cog.: Procognitive.

Several clinical studies have demonstrated that adjunctive treatment with 5-HT_{1A} partial agonists improves the cognitive state of schizophrenics [105]. Indeed, when tandospirone was administered to patients treated with typical antipsychotics, such as haloperidol, they performed better in tests of executive function, verbal learning and memory [112,113]. By contrast, when buspirone was co-administered with atypical antipsychotics, only modest improvements in attention were observed [114]. Differences between these studies may arise from the higher receptor selectivity and agonist efficacy of tandospirone and/or from the co-administration of typical versus atypical antipsychotics [105]. Nevertheless, taken together, these studies provide support for the contention that 5-HT_{1A} agonism is a promising strategy in improving the cognitive state of schizophrenia. In this context, F15599 was tested in rodent models of cognitive impairment induced by the noncompetitive NMDA receptor antagonist, phencyclidine (PCP), because NMDA receptor hypo-function, particularly in cortical regions, is considered to underlie aspects of negative symptomatology and cognitive deficits in schizophrenia [115–117]. F15599 exhibited favorable effects upon chronic treatment in a rat reversal-learning test [100]. In this test, animals are required to associate a stimulus with one of two levers of an operant box in order to receive food reinforcement. The reacquisition of the task following rule reversal provides a measure of cognitive flexibility and is disrupted by PCP administration. F15599 significantly increased the PCP-treated animals' rates of correct responding, whereas F13714 failed to reverse the PCP-induced deficit and, in fact, tended to accentuate it [100]. This observation is likely related to F13714's preferential presynaptic 5-HT_{1A} agonism, potently inhibiting 5-HT release [107]. Indeed, reversal learning is known to require functional serotonergic transmission in the frontal cortex [118,119] as well as functional D_2 receptors [120], suggesting that F15599 is able to re-establish normal functioning in this brain region through its preferential activity at cortical 5-HT_{1A} receptors at doses that elicit dopamine release without suppressing serotonergic neurotransmission. In another test of PCP-induced cognitive deficits, F15599 improved performance of rats in a hole-board test. The hole-board consisted of an open arena whose floor was fitted with 16 holes, four of them baited with food pellets. F15599 increased the proportion of visits to baited holes by PCP-treated animals, thus significantly improving working and reference memory scores [100], possibly by opposing the release of glutamate elicited in the frontal cortex by NMDA receptor blockade [121,122]. By contrast, F13714 disrupted performance when tested by itself and tended to accentuate PCP-induced deficits [123]. Finally, in an extensive study of the role of 5-HT_{1A} agonism on PCP-disrupted novel object recognition in rats, F15599 markedly improved the discrimination index, as did another efficacious agonist, tandospirone, whereas the partial agonist, buspirone, did not [Horiguchi M, Meltzer HY, Unpublished Data]. These observations parallel clinical data in which tandospirone, but not buspirone, attenuated cognitive deficits in schizophrenia (see earlier) [105].

In animal tests related to side effects, F15599 exhibited a superior profile compared with F13714. Thus in rats, F15599 exhibited little propensity to elicit forepaw treading or flat body posture, which are elements of 5-HT behavioral syndrome commonly observed with 5-HT_{1A} receptor agonists [124,125]. F15599 only elicited these responses at doses that were 30–60-fold higher than those that suppress immobility in the FST [99]. Furthermore, at antidepressant doses, F15599 did not impair performance in a two-lever delayed non-matching to position (DNMTP) test of working memory in which rats are required to press on the 'opposite' pedal to that which was previously presented; it did not interfere with performance in the 5-choice serial reaction time test (5CSRTT) in which rats were required to maintain a high level of sustained attention and respond to a stimulus light in order to gain a food reward; and it did not disrupt prepulse inhibition of startle response, a measure of sensory-motor gating [123]. By contrast, F13714 potently elicited these side effects at doses similar to those active in the FST.

The superior profile of F15599 could be related to differential occupancy of subpopulations of 5-HT_{1A} receptors. Indeed, using [^{3}H]WAY100635 as a radiotracer, F15599 occupied mouse cortical and hippocampal 5-HT_{1A} receptors *in vivo* nearly as potently as F13714 [99], despite the fact that the latter has greater affinity *in vitro* **(Table 3)** [98]. Interestingly, the dose–response curve of F15599 was noticeably shallower than that of F13714, suggesting that F15599 may distinguish different populations of receptors, possibly reflecting different coupling states. Further, in a PET imaging study, [^{18}F]F15599 preferentially labeled rat cortical, rather than hippocampal, 5-HT_{1A} receptors, even though the latter brain region expresses higher levels of receptors [101]. In cats, [^{18}F]15599 preferentially labeled 5-HT_{1A} receptors in the cingulate

cortex, whereas labeling was not observed in the hippocampus. This unique regional distribution of labeling differs sharply from that observed with antagonist radioligands such as [^{18}F]MPPF [126] or [O-methyl-^{11}C]WAY100635 [127], which label all 5-HT$_{1A}$ receptors in different brain regions. These observations support the notion that [^{18}F]F15599 preferentially interacts with specific subpopulations of 5-HT$_{1A}$ receptors in the brain, possibly depending on their coupling to specific G-protein subtypes. Two additional comments should be made: firstly, [^{18}F]F15599 also labeled mid-brain raphe 5-HT$_{1A}$ receptors in cats [101]. However, this interaction seems to be independent of agonist activity because, as discussed earlier, F15599 only inhibited raphe neuron electrical activity and hippocampal 5-HT release at high doses [102]. Secondly, F15599 may distinguish different populations of 5-HT$_{1A}$ receptors within cortical tissue – an assertion based on rat microinjection studies in which agonists were locally administered in the medial prefrontal cortex: F13714 and 8-OH-DPAT showed conventional monophasic dose–response relationships for inhibition of immobility in the FST (dose ranges from 0.016 to 8 µg), effects which were abolished by WAY100635. By contrast, microinjection of low doses of F15599 (0.016–1 µg) resulted in a V-shaped dose–response curve of immobility in the FST (~50% inhibition of immobility at 0.25 µg), an effect that was antagonized by WAY100635. Higher doses of F15599 (1–32 µg) resulted in a progressive decrease in immobility in the FST (>70% at 32 µg), which was also reversed by WAY100635 [128]. F15599 may, possibly, distinguish cortical 5-HT$_{1A}$ receptors expressed on pyramidal cells from those expressed on GABAergic interneurons [47,129].

Conclusion & future perspective

Serotonin 5-HT$_{1A}$ receptors constitute attractive targets for the management of a variety of neurological, psychiatric and pain disorders. However, they are expressed in a variety of brain regions where they mediate diverse and sometimes opposing functions. Therefore, considerable benefits could be gained by designing agonists that preferentially activate 5-HT$_{1A}$ receptor subpopulations in the specific brain regions that are relevant to the pathology of interest. Such preferential targeting may be achievable thanks to the distinct signal transduction mechanisms that are associated with 5-HT$_{1A}$ receptors in different brain regions. Some agonists have, in fact, been reported to exhibit preferential activation for specific signaling responses. In particular, the pharmacological profile of F15599 demonstrates that subpopulations of cortical 5-HT$_{1A}$ receptors may be pharmacologically targeted by biased (or 'functionally selective') agonists that possess specific intracellular 'signaling fingerprints', possibly via preferential Gαi G-protein subtype activation and/or potent ERK1/2 activation. Preferential targeting of cortical 5-HT$_{1A}$ receptors is a particularly attractive strategy because it should accelerate the onset of therapeutic efficacy in depression and attenuate impairments of working memory and cognitive flexibility observed in schizophrenia. In addition, preferential targeting of cortical 5-HT$_{1A}$ receptors may increase the therapeutic margin with respect to side effects that arise from the activation of other 5-HT$_{1A}$ receptor subpopulations. Taken together, these findings provide substantial evidence that the activity of 5-HT$_{1A}$ receptor agonists at distinct pre- and post-synaptic subpopulations of 5-HT$_{1A}$ receptors should be considered when selecting drugs that influence serotonergic neurotransmission.

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