Published in final edited form as:
Psychopharmacology (Berl). 2011 February ; 213(2-3): 265–287. doi:10.1007/s00213-010-2097-z.

The role of serotonin receptor subtypes in treating depression: a review of animal studies

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Abstract

Rationale—Serotonin reuptake inhibitors (SSRIs) are effective in treating depression. Given the existence of different families and subtypes of 5-HT receptors, multiple 5-HT receptors may be involved in the antidepressant-like behavioral effects of SSRIs.

Objective—Behavioral pharmacology studies investigating the role of 5-HT receptor subtypes in producing or blocking the effects of SSRIs were reviewed.

Results—Few animal behavior tests were available to support the original development of SSRIs. Since their development, a number of behavioral tests and models of depression have been developed that are sensitive to the effects of SSRIs, as well as to other types of antidepressant treatments. The rationale for the development and use of these tests is reviewed. Behavioral effects similar to those of SSRIs (antidepressant-like) have been produced by agonists at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_4, and 5-HT_6 receptors. Also, antagonists at 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 receptors have been reported to produce antidepressant-like responses. Although it seems paradoxical that both agonists and antagonists at particular 5-HT receptors can produce antidepressant-like effects, they probably involve diverse neurochemical mechanisms. The behavioral effects of SSRIs and other antidepressants may also be augmented when 5-HT receptor agonists or antagonists are given in combination.

Conclusions—The involvement of 5-HT receptors in the antidepressant-like effects of SSRIs is complex and involves the orchestration of stimulation and blockade at different 5-HT receptor subtypes. Individual 5-HT receptors provide opportunities for the development of a newer generation of antidepressants that may be more beneficial and effective than SSRIs.

Keywords

Serotonin; Receptors; Antidepressant; Anxiety; Depression

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, paroxetine, citalopram, and escitalopram are members of the frontline class of antidepressant treatments and exert their primary pharmacological effects through manipulation of the 5-HT system. Prior to the introduction of SSRIs, depression was treated using tricyclic drugs which inhibit the reuptake of monoamines or monoamine oxidase inhibitors (MAOIs) which inhibit their enzymatic degradation. By comparison with these older drugs, SSRIs became clinically successful because they reduced the frequency and severity of side effects that were potentially harmful and often required patients to withdraw from treatment. SSRIs selectively block 5-HT transporters (Sanchez and Hyttel 1999), thereby increasing

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extracellular concentrations of 5-HT at all of the postsynaptic 5-HT receptors. When given chronically, SSRIs maintain or further increase extracellular levels of 5-HT (Ceglia et al. 2004). In addition, a complex array of neuropharmacological changes, such as desensitization of 5-HT autoreceptors (Pineyro and Blier 1999), desensitization of 5-HT transporters (Frazer and Benmansour 2002), downregulation of neurotransmitter receptors (Caldecott-Hazard and Schneider 1992), changes in signal transduction (Tardito et al. 2006), mobilization of neurotrophins (Duman and Monteggia 2006), and increases in hippocampal neurogenesis (Sahay et al. 2007), emerge after chronic treatment with SSRIs that may also be involved in their clinical efficacy.

The introduction of SSRIs, starting with the approval of fluoxetine in 1987, revolutionized the behavioral pharmacology of antidepressant drugs (ADs). The behavioral effects of SSRIs were not detectable in many of the early animal models of depression or antidepressant tests, such as apomorphine-induced hypothermia, reserpine-induced ptosis or hypothermia, or the original forced swim test, because these tests were established for detecting the effects of tricyclics or MAOIs on catecholamine mechanisms (Porsolt et al. 1979). The absence of effects of SSRIs on the accepted animal models for depression at the time helped fuel skeptical concerns over whether drugs with selective pharmacological effects on serotonin would be good antidepressants (Welch 1995; Wong et al. 2005). Yet, after the SSRIs were introduced and their clinical efficacy became accepted, the effects of SSRIs were demonstrated to be active in a number of newer behavioral tests and animal models. Because these newer tests have established a broader pharmacological basis for their validity and specificity for depression, i.e., they are sensitive to tricyclics, MAOIs, SSRIs electroconvulsive shock, and other somatic treatments for depression, they have displaced the earlier tests for antidepressants for use in drug discovery.

The overall goal of this review is to understand more precisely how 5-HT participates in producing the antide-pressant effects of SSRIs from the standpoint of animal behavioral pharmacology studies. SSRIs initiate antidepressant effects by increasing extracellular 5-HT levels at all postsynaptic 5-HT receptors. However, at least 14 serotonin (5-HT) receptor subtypes belonging to seven major families have been identified in brain and their receptors have distinct topographical distributions and cell signaling mechanisms (Table 1). The nuclei of serotonin-producing neurons in the hindbrain and midbrain and their axonal projections have been identified and the receptors responsible for interactions with other neurotransmitters have been extensively mapped (Barnes and Sharp 1999; Hannon and Hoyer 2008). Detailed pharmacological and behavioral information exists concerning the effects of prototypic 5-HT receptor agonists and antagonists and mice with genetic mutations of different 5-HT receptors. Using rodent tests for antidepressants and models of depression that are sensitive to SSRIs as a platform, this review will examine the role of 5-HT receptor subtypes in the behavioral response to SSRI antidepressants. The original goals of these studies were to identify a particular 5-HT receptor subtype responsible for the clinical effects for SSRIs, develop newer compounds lacking the side effects of SSRIs, or understand treatment resistance by determining the receptors that block the effects of SSRIs. However, it is now clear that multiple 5-HT receptor subtypes participate in the therapeutic effects of SSRIs in treating depression and anxiety and it is not clear whether one is more important than another. Surprisingly, agonists and antagonists at some 5-HT receptors produce antidepressant-like behavioral effects, although their exact mechanisms may differ. Furthermore, some 5-HT receptors may have become attractive targets for the development of novel antidepressants, alone or in combination with other drugs, because they may lead to more beneficial behavioral effects than the SSRIs.

Behavioral pharmacology of SSRIs

This section will describe behavioral pharmacology studies in rodents that helped to establish the role of the 5-HT system in the treatment of depression. Behavioral tests of depression can be segmented into two categories, acute and chronic, based on the duration of drug treatment. First, acute tests, or behavioral tests in which the effects of SSRIs are evident after a single or small number of administrations, will be reviewed. This will be followed by a review of models of depression and behavioral tests in rodents that require chronic (≥2 weeks) treatment.

Acute tests

Forced swim test—The forced swim test (FST) was developed by Porsolt et al. as a model of depression that measured the effects of antidepressant compounds in rats (Borsini and Meli 1988;Porsolt et al. 1977b). The FST is more commonly thought of now as a behavioral test in rodents rather than a model of depression, and measures behavioral patterns of the response to stress that are correlated with either increased vulnerability to stress or treatments for depression (Cryan et al. 2005c). The test involves placing the rat in a container of water (usually cylindrical) from which it is unable to escape. Initially, the rat attempts to escape, but eventually adopts a posture of immobility (passive behavior), characterized by the lack of movement except that which is necessary to keep the rat's nose above the water level. The test consists of two swim exposures. The first is a 15-min exposure. The second, conducted 24 h later, is a 5-min exposure. Immobility time is the main measure recorded during the second 5-min test. In the FST, antidepressants decrease the time spent immobile by increasing active coping behaviors. These effects are relatively selective for antidepressants as a class and do not involve increased general locomotor activity, unlike psychomotor stimulants (e.g., amphetamine and cocaine). The FST is the most frequently used behavioral test for measuring the effects of different classes of antidepressants or evaluating the effects of mutant rodents on depression-related behaviors. Treatments which increase vulnerability to depression can produce the opposite effect of ADs, or increases in immobility (Cryan et al. 2005c).

Motivated by the inability of the FST to measure the effects of SSRIs (Borsini 1995; Porsolt et al. 1979), Lucki et al. introduced changes in the procedure and scoring of the rat FST (Detke and Lucki 1996; Detke et al. 1995a). The most important modifications (e.g., deeper water, larger cylinder) allowed for free swimming and the identification of component active behaviors in addition to immobility. The original FST scored only the total time spent immobile. In the modified rat FST, a scoring system was introduced that measured the frequencies of swimming and climbing over the 5-min test (Detke et al. 1995a). Swimming is defined as horizontal movement throughout the chamber and climbing is defined as vertical movement of the forepaws directed towards the sides of the chamber. Thus, the modified rat FST distinguishes between passive responses (immobility) and active responses (increases in swimming or climbing) to stress (Cryan et al. 2005c). Antidepressants acting through the serotonergic system, including the SSRIs fluoxetine, sertraline, paroxetine, and citalopram, selectively increased swimming behavior. In addition, the modified rat FST differentiated between antidepressants that work through serotonergic mechanisms or noradrenergic mechanisms, as noradrenergic compounds selectively increased climbing behavior (Detke et al. 1995a) and drugs with dual effects increased both swimming and climbing (Reneric and Lucki 1998). The modified rat FST is sensitive to all major classes of antidepressants and somatic treatments of depression and has been used by many laboratories (Cryan et al. 2005c). Fluoxetine also reduces immobility and increases swimming behavior in the FST after chronic administration, although low drug doses that

are initially inactive become effective with chronic treatment (Cryan et al. 2005b; Detke et al. 1997).

The FST is also used widely to measure the effects of SSRIs in mice. Although laboratories have followed a number of different procedures (David et al. 2003; Lucki et al. 2001; Porsolt et al. 1977a), a major determinant of the response to SSRIs is the strain of mouse. Recently, the effects of chronic administration of fluoxetine given to BALB/c mice were measured in the FST using a more precise behavioral rating procedure (i.e., measuring swimming and climbing behaviors) that was similar to the procedure described previously for rats (Holick et al. 2008).

Tail suspension test—The tail suspension test (TST) was developed as a simpler and faster way to test the behavioral response to antidepressants in mice based on a similar behavioral principal as the FST (Steru et al. 1985). In the test, mice are attached and suspended from a bar by their tails with adhesive tape. The amount of time the mouse spends immobile during the 6-min test is interpreted as a measure of depression-like behavior. The TST has many advantages over the FST including the lack of hypothermic effects of cold water, the ability to test strains that may have motor deficits that make swimming difficult and increased sensitivity to a wider range of antidepressant compounds (Cryan et al. 2005a; Petit-Demouliere et al. 2005). Several mouse strain surveys have been conducted on the behavioral response of antidepressants in the TST (Bai et al. 2001;Crowley et al. 2005; Ripoll et al. 2003; van der Heyden et al. 1987). Although there is some disagreement on test conditions and results between laboratories, possibly due to supplier differences, all laboratories reported important strain differences in the response to SSRIs. The BALB/c, NMRI, and the outbred NIH Swiss strains appear the most responsive to SSRIs.

DRL behavior—Operant behavior maintained under a differential-reinforcement-of-low-rate schedule that reinforces responses with inter-response times greater than 72 s (DRL 72 s) demonstrates a unique sensitivity to ADs. Acute administration of ADs from various pharmacological classes, including SSRIs, reduce response rate and increase reinforcement rate of rats responding under this schedule (O'Donnell et al. 2005). This pattern of response is unique to ADs and not produced by any other drugs from other psychotherapeutic classes. Although DRL behavior is a marker for AD-like behavioral effects in rodents, it is unclear why antidepressants produce this pattern of behavior. Interestingly, depletion of 5-HT produced a disruption of the timing, or the opposite effect of antidepressants, on behavior maintained under the DRL 72-s schedule (Jolly et al. 1999).

Drug discrimination—Drug discrimination techniques, where rats are trained to respond for food reward on a particular lever only when administered a training drug, allow the interoceptive properties of drugs to be studied. This technique has been used most often for studying drugs of abuse. The SSRI citalopram has been trained as a discriminative stimulus and other SSRIs, sertraline and paroxetine, but not diazepam or clozapine fully substituted for citalopram (Millan et al. 1999). Other groups have also shown successful training of SSRIs as discriminative stimuli (Kreiss and Lucki 1994; Marona-Lewicka and Nichols 1998; Wolff and Leander 1999) and their stimulus effects did not generalize to selective norepinephrine reuptake inhibitors. Although discriminative stimulus properties of ADs can be used to identify and study compounds with neuropharmacological similarities, the basis for their similarity cannot be shown to be related to their AD properties (Dekeyne and Millan 2003).

Chronic tests of antidepressants and models of depression

Chronic mild stress—The rationale for the chronic mild stress (CMS) model is that increased exposure to environmental stressors, particularly unpredictable and uncontrollable stressors, increases the likelihood that a person will develop depression (Kendler et al. 2004). In order to reproduce unpredictable stressors in the laboratory, researchers typically use a set of mild stressors (e.g., strobe lighting, soiled cages, modified light cycles, etc.) administered in an irregular fashion in order to mimic the stress of everyday life and prevent habituation to the stressors (Willner 1997; 2005). A number of groups have shown that CMS procedures can lead to behavioral and endocrine changes in rats and mice that appear similar to human depression when administered over a period of weeks. The most common behavioral output measured during CMS experiments is the presence of anhedonia represented by decreased consumption of a sweetened water solution. However, changes in FST behavior, sleep alterations, grooming, and locomotor activity suggest that the pathological changes resulting from CMS are more comprehensive and model more directly many of the symptoms of depression (Willner 2005).

The alterations caused by CMS can be reversed by chronic treatment with a number of ADs in rats and mice, especially the SSRIs fluoxetine, sertraline, and citalopram (Jayatissa et al. 2006; Marona-Lewicka and Nichols 1997;Muscat et al. 1992; Yalcin et al. 2008). Another intriguing feature of CMS is that not all rodents exposed to CMS show a pathological change in behavior and not all CMS-responsive animals show a reversal after treatment with antidepressants (Jayatissa et al. 2006). This feature of differential vulnerability is present in human depression, as not all people respond equally when presented with the same stressor (Kendler et al. 2004) and a high percentage of patients do not respond to antidepressant treatment (Rush et al. 2006). The inter-animal variability provides opportunities for research into the neural underpinnings of stress vulnerability and treatment resistance.

A major hindrance to the universal application of CMS in depression research is the difficulty of reproducing antidepressant effects between laboratories. A number of laboratories have been successful in the use of CMS (reviewed by Willner 2005), but others have had difficulty implementing the procedure. Reproducibility issues may be due to the lack of a standardized stress protocol, genetic background, and differences in animal husbandry (e.g., colony room space/size, ventilation, and handling; Cryan and Slattery 2007).

Olfactory bulbectomy—Bilateral removal of the olfactory bulbs causes severe behavioral and endocrine changes in rodents that have been used as a model of depression (Song and Leonard 2005). The pathological changes observed after olfactory bulbectomy (OB) is not the result of anosmia, as peripheral blockade of olfactory receptors does not result in an analogous syndrome (Calcagnetti et al. 1996). The most common behavioral change monitored in the OB model is hyperactivity in an open field apparatus. These changes can be reversed by chronic antidepressant drug treatment, including the SSRIs fluoxetine, paroxetine, sertraline, and fluvoxamine (Song and Leonard 2005). Other behavioral changes caused by OB appear to model some of the cognitive, hedonic, or motivational deficits found in humans with depression (Hall and Macrides 1983; Pandey et al. 2010; Vieyra-Reyes et al. 2008). The OB procedure causes degeneration in a number of regions that project to and receive projections from the olfactory bulbs, such as the amygdala and hippocampus (Carlsen et al. 1982). OB causes neuronal loss in the raphe nuclei, which may contribute to abnormal serotonergic neurotransmission following the procedure (Nesterova et al. 1997). Recent evidence that humans with depression may exhibit higher olfactory detection thresholds compared to controls and performance in olfactory

tasks is inversely correlated with depression severity (Pause et al. 2001) provides more evidence that the OB model may share a number of core features with depression.

Novelty-suppression of feeding/novelty-induced hypophagia—Both the novelty-suppression of feeding (NSF) and novelty-induced hypophagia (NIH) procedures are tests of hyponeophagia that utilize the rodent species' natural aversion to bright, open spaces and novelty to decrease approach toward palatable food. The tests measure the latency to approach food and amount of food consumed in a novel arena (Shephard and Broadhurst 1982). The NSF test uses food deprivation to drive consumption (Bodnoff et al. 1988; Shephard and Broadhurst 1982) whereas the NIH test uses palatable foods (usually sweetened) that are consumed without food deprivation (Bechtholt et al. 2008;Dulawa and Hen 2005). The NIH procedure removes the stress of food deprivation but requires a training phase in order to produce stable food consumption levels (Bechtholt et al. 2008). Exposure to the novel arena increases approach latency and decreases food consumption compared to their home cage. Anxiolytic drugs, such as benzodiazepines, decrease approach latency and increase food consumption in the novel arena without altering home cage behavior (Bodnoff et al. 1988; Merali et al. 2003). SSRIs, when administered chronically to rats and mice, are also able to produce an anxiolytic-like effect in these tests (Bechtholt et al. 2008; Bodnoff et al. 1988; Bodnoff et al. 1989; Dulawa et al. 2004). Under some circumstance, the production of this behavioral effect has been associated with increased hippocampal neurogenesis because the disruption of hippocampal neurogenesis by exposure to radiation prevented chronic SSRIs from reducing the hyponeophagia response (David et al. 2009; Santarelli et al. 2003). The NIH response to chronic fluoxetine was also associated with increases in brain-derived neurotrophic factor (BDNF) levels in the hippocampus and frontal cortex (Balu et al. 2009; Hodes et al. 2010). The NSF and NIH tests are one of the few behaviors sensitive to the anxiolytic effects of chronic AD treatment (Borsini et al. 2002).

Chronic social defeat—Affective disorders have been proposed to involve exaggerated and persistent displays of signs of subordination from social stress, reduced social status, and persistent threats from the social environment (Rygula et al. 2005). Several behavioral paradigms have been developed in rodents for examining the effects of AD treatments on social stress. Rats stressed socially for weeks using an intense and prolonged resident–intruder paradigm demonstrated reduced locomotor activity, sucrose preference, and increased immobility time in the FST. Chronic citalopram or fluoxetine normalized behaviors related to motivation and reward sensitivity (Rygula et al. 2006). Mice exposed to daily long and intense bouts of social defeat followed by continuous protected sensory contact with their aggressor for weeks develop a display of intense aversive responses and spend less time interacting with another mouse. Chronic administration of fluoxetine or imipramine for 4 weeks improved social interaction in defeated animals (Berton et al. 2006).

A method for measuring social competition involves allowing two food-deprived mice to develop stable dominant-subordinate dyads by competing for limited access to food in a narrow tube. Administration of fluoxetine or imipramine chronically to the subordinate mouse caused reversal of the food dominance (Malatynska and Knapp 2005).

Learned helplessness—Learned helpless is a theory of depression where animals exposed to inescapable stress develop neurovegatative and behavioral changes that are similar to human depression, such as rapid eye movement sleep alterations, reduced body weight, diminished sexual behavior, and elevated corticotropin releasing factor (CRF) and corticosterone levels (Maier and Seligman 1976; Weiss et al. 1981). In learned helplessness studies, animals exposed to inescapable stress subsequently fail to escape from a situation where escape is possible. Studies have been done using a shuttle box escape or bar-pressing response and electric shock to produce helplessness. Animals are compared to several

control groups, including yoked control animals that receive the same amount of shock but are allowed to terminate the shock through a response. Differences are then attributable to control over shock termination. Repeated treatment with SSRIs reduced the latency to escape or decreased the number of animals that develop learned helplessness (Petty et al. 1996; Valentine et al. 2008; Zazpe et al. 2007).

Hippocampal neurogenesis, neurotrophin mobilization, and neuroplasticity— The neurotrophic hypothesis of depression postulates that reductions in the function of neurotrophins, that ordinarily support neurogenesis, survival, and neuronal plasticity in the adult brain, is associated with the pathogenesis and treatment of depression (Duman and Monteggia 2006;Sahay and Hen 2007). This hypothesis proposes that successful antidepressant treatments are associated with an enhancement in hippocampal neurogenesis, increase of neurotrophin levels, and resulting increase in hippocampal function as measured by neuronal response or behavior following chronic administration. SSRIs have played an important role in supporting the neurotrophic hypothesis of depression because chronic administration of fluoxetine or citalopram, along with other ADs and electroconvulsive shock, increases hippocampal cell proliferation (Balu and Lucki 2009; Malberg et al. 2000) and increases the expression of BDNF (Nibuya et al. 1995). In addition, chronic administration of SSRIs counteracts the effects of stress in rats and mice (David et al. 2009; Jayatissa et al. 2006). Ablation of adult neurogenesis in mice blocked the effects of chronic fluoxetine in the NSF paradigm or in the modified rat FST (Airan et al. 2007; Santarelli et al. 2003). Nevertheless, the role of hippocampal neurogenesis in causing depression is debatable because, by itself, the reduction of neurogenesis does not appear to cause a depressive phenotype (Lucassen et al. 2010; Sahay and Hen 2007).

Role of endogenous 5-HT transmission in the behavioral effects of SSRIs

Deficiencies in 5-HT metabolism have often been associated with clinical depression and suicide (Maes and Meltzer 1995; Mann 2003), supporting a role for 5-HT in the pathogenesis of depression. However, behavioral studies in rodents have generally not been successful at producing a depressive behavioral phenotype by reducing 5-HT synthesis. Pharmacological depletion of 5-HT, by the administration of the tryptophan hydroxylase (TPH) inhibitor parachlorophenylalanine (PCPA) has been used by a number of research groups in order to determine whether the disruption of 5-HT synthesis in rodents produces behavioral depression in tests of antidepressant efficacy. 5-HT depletion did not produce effects on baseline behavior in the FST in rats or mice (Gavioli et al. 2004; O'Leary et al. 2007; Page et al. 1999). In addition, the destruction of 5-HT neurons using neurotoxins did not increase baseline immobility in the rat FST (Lucki et al. 1994).

Recently, a depressive behavioral phenotype has been reported for mice with mutations in the genes for TPH (*tph1* and *tph2*). Two genes regulate 5-HT synthesis, with *tph1* localized predominantly to peripheral tissues (Walther and Bader 2003) and a second gene (*tph2*) encoding the 5-HT-synthesizing enzyme in neurons (Walther et al. 2003). Mice with deletions of both genes regulating 5-HT synthesis (*tph1* and *tph2*), producing a nearly complete depletion of 5-HT content, or TPH2 knockout (KO) mice, with a substantial but incomplete depletion of 5-HT, were significantly more immobile than wild-type mice in the TST (Savelieva et al. 2008). A second group generated a TPH2 knock-in mouse line expressing a mutant form of the protein and, with reduced TPH activity and an 80% reduction in brain 5-HT, was also reported to have significantly increased immobility times in the TST (Beaulieu et al. 2008). The depressive behavioral phenotype in the TPH genetic models may result from the absence of 5-HT because the magnitude of tissue 5-HT depletion in the mouse was larger than achieved with PCPA although neither study attempted to reverse the phenotype by administering 5-HT precursors. Alternatively, the

depressive phenotype of both constitutive TPH genetic models may be due to a key role of 5-HT during development. Although not due to nonspecific effects on locomotor activity, the models of genetic 5-HT depletion should be studied with other antidepressant tests or depression models to establish their specificity. Nevertheless, these genetic preparations may now provide an important way to identify the pathological role of 5-HT depletion in depressive behavior.

Mouse strain differences in a C1473G polymorphism in the *tph2* gene have been shown to alter the rate of 5-HT synthesis and have been investigated as a source of variation in the behavioral effects of SSRIs. Although the 1473C allele is highly conserved across the species, the 1473G form is found in several inbred mouse strains and confers a significant reduction in brain serotonin synthesis and tissue content (Cervo et al. 2005; Zhang et al. 2004). Some murine studies suggest that the C1473G polymorphism in *tph2* modifies the behavioral response to SSRIs in the FST (Cervo et al. 2005; Guzzetti et al. 2008). They reported that C57BL/6 and 129Sv mice, two strains carrying the 1473C allele, responded best to acute SSRI treatment in the FST, whereas two strains with the 1473G allele, BALB/c and DBA/2 mice, were refractory to the effects of SSRIs. However, these findings have not been replicated by other laboratories or using responses to SSRIs other than the FST (Crowley et al. 2005; Crowley et al. 2006; Holick et al. 2008; Lucki et al. 2001; Miller et al. 2008). Recently, congenic lines of C57BL/6 and BALB/c mice were generated for the C1473G polymorphism, allowing the role of the polymorphism to be evaluated on each genetic background. Although the C1473G polymorphism determined differences in 5-HT synthesis, they did not differ in baseline response or in their response to escitalopram in the TST. Thus, other genes are likely play an important role in determining strain differences in the behavioral effects of SSRIs (Siesser et al. 2010).

Even though the depletion of 5-HT does not always produce behavioral depression, an intact 5-HT system remains an important prerequisite for efficacious treatment with SSRIs in the FST and TST. Depletion of 5-HT with PCPA blocks the effects of fluoxetine in the FST and TST, while the effects of desipramine, which acts primarily as a norepinephrine reuptake inhibitor, are unaffected by 5-HT depletion (Cesana et al. 1993;Gavioli et al. 2004; O'Leary et al. 2007; Page et al. 1999). These effects demonstrate that serotonergic mechanisms underlie the acute behavioral effects of SSRIs on tests of depressive behavior. The effects in rodent tests of depressive behavior correspond with a similar pattern of relapse induction in clinical patients following the depletion of 5-HT (Delgado 2004; Delgado et al. 1991). Depletion of 5-HT did not alter the effects of fluoxetine or paroxetine in LH (Zazpe et al. 2007).

5-HT also plays an integral role in the behavioral effects of compounds that do not exert their primary effects through manipulation of the 5-HT system. For example, nitric oxide is an intracellular messenger for a number of CNS receptors. Decreasing nitric oxide signaling by inhibiting nitric oxide synthase (NOS) has been shown to produce antidepressant-like effects in the rat FST. These behavioral effects are dependent on intact 5-HT synthesis because they are blocked by the depletion of 5-HT using PCPA (Harkin et al. 2003; Ulak et al. 2010). The administration of the mineral zinc has also been shown to produce antidepressant-like effects when administered alone or as a supplement to antidepressant treatment in a number of animal models and preliminary clinical studies (Kroczka et al. 2000; Nowak et al. 2003a; Nowak et al. 2003b). Pretreatment with PCPA blocks the antidepressant-like effects of zinc (Szewczyk et al. 2009). Interestingly, NOS inhibitors and zinc may work through a similar mechanism as they interact with the L-arginine–nitric oxide pathway (Rosa et al. 2003). Since SSRIs produce their behavioral effects through endogenous 5-HT, the ability to eliminate this mechanism would allow for other novel compounds to be differentiated from SSRIs.

5-HT receptor subtypes and the behavioral response to antidepressants—Over the years, a number of ligands selective for individual 5-HT receptor subtypes, both agonists and antagonists, have been used as pharmacological tools in order to delineate the behavioral functions of individual 5-HT receptors. A description of these receptors, their signaling pathways, and localization in brain is delineated in Table 1. Also, mice with genetic deletion of specific 5-HT receptors or the 5-HT transporter have been examined for behavioral alterations on tests related to antidepressant drug activity or the effects of SSRIs. These mice may be models for how genetic polymorphisms of 5-HT receptors in humans may influence the therapeutic effects of SSRIs. This section will review the literature concerning the effects of modulating the function of individual 5-HT receptors on rodent behavioral tests for ADs and models of depression. The findings are summarized in Table 2.

5-HT_{1A} receptor—5-HT_{1A} receptors (Table 1) were identified initially as the spiperone sensitive portion of [^{3}H]5-HT binding and later confirmed using the subtype selective agonist [^{3}H]8-OH-DPAT as a radioligand (Hannon and Hoyer 2008). Mapped extensively by receptor autoradiography using several subtype selective ligands, the density of 5-HT_{1A} receptors is high in limbic brain areas, such as the hippocampus, lateral septum and the cortex, where they are located postsynaptic to 5-HT neurons. These receptors located in the septum regulate cholinergic release (Jeltsch-David et al. 2008), in the prefrontal cortex regulate glutamate release (Lopez-Gil et al. 2010), and in the ventral tegmental area regulate dopamine release (Di Matteo et al. 2008). The principal signaling mechanism in these regions is coupling to $G_{i/o}$ to inhibit adenylate cyclase activity, although other signaling pathways have been described. 5-HT_{1A} receptors are also located on the soma and dendrites of 5-HT containing neurons in the brainstem and medullary raphe nuclei where their stimulation inhibits neuronal firing, 5-HT synthesis, and release at terminals. 5-HT_{1A} receptors have been associated with anxiety, depression, temperature regulation, corticosterone secretion, and learning and memory. Buspirone and ipsapirone are partial 5-HT_{1A} receptor agonists marketed for the treatment of anxiety. Deficits in 5-HT_{1A} receptor function have been reported in depressed patients (Savitz et al. 2009) and a polymorphic allele in the 5-HT_{1A} receptor promoter region in humans (C1019G) has been identified as a risk allele for depression and anxiety disorders and resistance to the effects of SSRIs (Le Francois et al. 2008).

There is a large body of evidence that 5-HT_{1A} receptor agonists produce antidepressant-like effects (Table 2) across a number of different tests in animals (Blier and Ward 2003; De Vry 1995). A number of 5-HT_{1A} receptor agonists, including the prototypical 5-HT_{1A} receptor agonist 8-OH-DPAT and partial 5-HT_{1A} receptor agonists buspirone and ipsapirone, decrease immobility in the rat FST (Cryan et al. 2005c; Kostowski et al. 1992; Lucki et al. 1994; Singh and Lucki 1993). Also, the effects of 5-HT_{1A} receptor agonists in the rat FST are blocked by pretreatment with 5-HT_{1A} receptor antagonists (Cryan et al. 2005c;Detke et al. 1995b).

The AD-like effects of 5-HT_{1A} receptor agonists are not confined to the FST. Alnespirone and VN2222, a 5-HT_{1A} agonist and a mixed reuptake inhibitor and 5-HT_{1A} agonist, respectively, have been shown to produce AD-like effects in the LH paradigm (Mac Sweeney et al. 1998; Tordera et al. 2002). The 5-HT_{1A} receptor agonists produce AD-like effects in rats responding under the DRL 72-s schedule (O'Donnell et al. 2005). Chronic treatment with the partial agonist buspirone produced AD-like effects in the CMS paradigm (Przegalinski et al. 1995) and chronic flesinoxan produced AD-like effects in the OB model (Cryan et al. 1997). Chronic administration of the 5-HT_{1A} receptor agonists 8-OH-DPAT or buspirone also reduces approach latencies in the NIH test and increases neurogenesis and survival of new neurons in the dentate gyrus after chronic treatment in rats and mice and (Banasr et al. 2004; Bodnoff et al. 1989; Santarelli et al. 2003). Nevertheless, with the

exception of buspirone and ipsapirone, the development of 5-HT_{1A} receptor agonists as antidepressants has not been clinically successful (Blier and Ward 2003).

Chronic administration of SSRIs and other ADs modifies the response of postsynaptic and presynaptic 5-HT_{1A} receptors in a number of brain regions. Electrophysiological studies have shown that chronic administration of ADs and electroconvulsive shock facilitate transmission through 5-HT_{1A} receptors in limbic regions, like the hippocampus (Burnet et al. 1995; Chaput et al. 1991; Haddjeri et al. 1998; Shen et al. 2002), emphasizing the importance of postsynaptic 5-HT_{1A} receptors in the antidepressant response. It has also been postulated that desensitization of 5-HT_{1A} autoreceptors after weeks of treatment with antidepressant drugs is a key factor in permitting enhanced transmission to develop at postsynaptic regions and can account for the delay between the commencement of treatment and the alleviation of depressive symptoms (Pineyro and Blier 1999). Because antagonism of 5-HT_{1A} autoreceptors in the raphe nuclei could facilitate AD-like effects through disinhibition of 5-HT release, 5-HT_{1A} receptor antagonists were proposed as a promising adjunct to traditional AD treatment (Artigas et al. 1996). This principle spurred the strategy of combining pindolol, a partial agonist at 5-HT_{1A} and 5-HT_{1B} receptors, with various ADs as an adjunct for treatment-resistant depression or to initiate a more rapid onset of response (Artigas et al. 2001). Some animal studies simulated the facilitation of combining pindolol with SSRIs or other ADs in rodent behavioral tests (Cousins and Seiden 2000; Cryan et al. 2005c; Millan et al. 1998), although not all studies were successful (Tatarczynska et al. 2004). Some showed dose-dependence where pindolol blocked the effects of SSRIs at higher doses indicating a potential trade-off between the blockade of presynaptic and postsynaptic receptors (Cryan et al. 2005c). Based on a principal similar to pindolol augmentation, the novel antidepressant vilazodone was developed to facilitate 5-HT transmission as a single drug that is a combined 5-HT_{1A} receptor partial agonist and SSRI. Vilazodone has been shown to produce greater increases of extracellular levels of 5-HT in the cortex and hippocampus than fluoxetine given alone in rats and also produced AD-like behavioral effects in the FST in rats and mice (Page et al. 2002). The significance of the higher 5-HT levels has not been yet been evaluated, although vilazodone was reported to be an effective antidepressant in one clinical trial (Rickels et al. 2009)

5-HT_{1A} KO mice have been generated under different genetic background and studied by multiple laboratories (Heisler et al. 1998; Parks et al. 1998). A common feature of 5-HT_{1A} receptor deletion was the emergence of an antidepressant-like and anxiogenic phenotype (Heisler et al. 1998; Jones and Lucki 2005a, b; Parks et al. 1998; Zhuang et al. 1999). This life-long phenotype was caused by the loss of the 5-HT_{1A} receptor during early development because mice spared from the deletion of 5-HT_{1A} receptors until after maturity did not demonstrate the anxiety phenotype (Gross et al. 2002). Although 5-HT_{1A} KO mice exhibit normal basal release of 5-HT, the absence of 5-HT_{1A} autoreceptors elevated the increase of 5-HT levels in response to fluoxetine, just as seen with 5-HT_{1A} receptor antagonists (Knobelman et al. 2001). Nevertheless, 5-HT_{1A} KO mice demonstrate refractory behavioral responses to acute or chronic SSRI treatment (Holick et al. 2008; Mayorga et al. 2001; Santarelli et al. 2003), probably because of the absence of postsynaptic 5-HT_{1A} receptors that are required for antidepressant behavioral responses.

More recently, mice with inducible suppression of presynaptic 5-HT_{1A} receptors under the control of the Pet-1 promoter were generated and tested for the response to stress and chronic antidepressant treatment (Richardson-Jones et al. 2010). The mice with a higher density of 5-HT_{1A} autoreceptors demonstrated enhanced response to stressors, including greater immobility in the FST and TST at baseline. Mice with a lower density of 5-HT_{1A} autoreceptors augmented the increase of extracellular 5-HT levels by fluoxetine in the hippocampus and responded more rapidly to chronic treatment on a test for hyponeophagia.

The results with these mice may provide a mechanistic model for the effects of 5-HT_{1A} receptor polymorphisms in humans on the risk for depression and focus the locus of the risk on presynaptic 5-HT_{1A} receptors.

Because 5-HT_{1A} receptors are located presynaptically in the dorsal and median raphe nuclei and distributed at widespread postsynaptic locations, there has been persistent debate about the location of 5-HT_{1A} receptors most important in responses to stress and antidepressant treatment. The administration of 8-OH-DPAT to rats locally into the dorsal raphe nucleus produced antidepressant-like effects in the FST, presumably by activating presynaptic 5-HT_{1A} receptors (Cervo et al. 1988). However, this assumption would be challenged by a recent demonstration that 5-HT_{1A} receptor mRNA in the dorsal raphe is also located in GABA neurons (Bonnavion et al. 2010). Local administration of 8-OH-DPAT into terminal regions in the lateral septum also produced antidepressant-like effects in the FST (Schreiber and De Vry 1993). Moreover, when 5-HT-producing neurons are destroyed or 5-HT synthesis is inhibited, 5-HT_{1A} receptor agonists still produce AD-like effects in the mouse or rat FST suggesting that the AD-like effects of 5-HT_{1A} receptor agonists are due to activation of postsynaptic 5-HT_{1A} receptors (Lucki et al. 1994; Matsuda et al. 1995). In conclusion, presynaptic 5-HT_{1A} receptors are associated with the risk for depressive behavior and their blockade augments the effects of SSRIs. Postsynaptic 5-HT_{1A} receptors are essential for producing the antidepressant-like effects of 5-HT_{1A} receptor agonists and possibly SSRIs.

5-HT_{1B} receptor—5-HT_{1B} receptors have a complex history, existing structurally as rodent and non-rodent species homologues with similar pharmacological profiles (Table 1) except for a few compounds (Hannon and Hoyer 2008). Their highest density is in the basal ganglia, nucleus accumbens, and substantial nigra, with substantial expression in many other regions, like the cingulate cortex, hippocampus, and amygdala. The 5-HT_{1B} receptor has a role as both an 5-HT autoreceptor at 5-HT terminals and a 5-HT heteroreceptor located on non-5-HT neurons to control the release of other neurotransmitters. 5-HT_{1B} receptors have been implicated in migraine, locomotor activity, aggression, drug reinforcement, depression, and anxiety (Sari 2004)

The 5-HT_{1B} receptor is a target for the pathophysiology of depression because it is regulated by exposure to environmental stress and exposure to antidepressants (Ruf and Bhagwagar 2009). The stress of the LH procedure causes an upregulation of the 5-HT_{1B} receptor in the cortex, hippocampus, septum, and dorsal raphe (Edwards et al. 1991; Neumaier et al. 1997). Chronic AD treatment decreases the mRNA of the 5-HT_{1B} receptor in the dorsal raphe and decreases the efficacy of 5-HT_{1B} autoreceptors, which may lead to an increase in 5-HT release (Anthony et al. 2000; Gur et al. 2000; Neumaier et al. 1996; Pineyro and Blier 1999). 5-HT_{1B} heteroreceptors on granule cells and pyramidal cells appear to contribute to increases of hippocampal neurogenesis, a marker of AD treatment (Banasr et al. 2004). Also, 5-HT_{1B} receptors are regulated by the binding protein p11, a protein that increases 5-HT_{1B} receptor function in a number of brain regions. Antidepressant treatment in mice increased p11 and transgenic overexpression of p11 produced antidepressant-like behavioral effects in mice (Svenningsson et al. 2006). Genetic deletion of p11 in mice caused depression-like behavioral effects, like increased immobility in the TST and FST, and p11 levels were reduced in brain tissue from depressed patients. Restoration of p11 expression in the nucleus accumbens of p11 KO mice normalized depression-like behaviors (Alexander et al. 2010).

The effects of systemic administration of 5-HT_{1B} receptor ligands on depression-related behavioral tests (Table 2) are mixed. The 5-HT_{1B} receptor agonists anpirtoline and CP 94253 produce AD-like effects in the FST in mice (Chenu et al. 2008; Tatarczynska et al. 2005). The effects of 5-HT_{1B} receptor agonists were blocked by genetic deletion of 5-HT_{1B}

receptors and by the antagonist SB 216641, but not by the depletion of 5-HT, suggesting the involvement of postsynaptic 5-HT_{1B} receptors. Additionally, the 5-HT_{1B} receptor antagonist GR127935 blocked the AD effects of citalopram and paroxetine suggesting that these drugs may exert some of their therapeutic effects through activation of the 5-HT_{1B} receptor (Chenu et al. 2008).

However, other studies suggest the involvement of presynaptic 5-HT_{1B} autoreceptors in AD-like effects. Combining the 5-HT_{1B} receptor antagonists GR 127935 or SB 216641 with paroxetine facilitated the AD-like effect of paroxetine in the forced swimming test in rats (Tatarczynska et al. 2002), but did not facilitate behavior when these antagonists were combined with fluoxetine or citalopram (Tatarczynska et al. 2002; Tatarczynska et al. 2004). Other laboratories have reported 5-HT_{1B} receptor antagonists, when given alone to increase extracellular 5-HT, produce AD-like behavioral effects and augment the effects of ADs (Dawson et al. 2006; Hogg and Dalvi 2004; Tatarczynska et al. 2004). These effects were probably due to the disinhibition of 5-HT release by blocking 5-HT_{1B} autoreceptors. The inconsistent pattern of results between studies are possibly due to the dual roles of 5-HT_{1B} receptors as heteroreceptors and terminal autoreceptors but may also involve species differences and procedural differences between laboratories.

A 5-HT_{1B} receptor knockout mouse has been generated that demonstrates increased aggression and reduced anxiety (Zhuang et al. 1999). Male 5-HT_{1B} KO mice did not exhibit an AD-like baseline response in the TST (Mayorga et al. 2001). 5-HT_{1B} KO mice showed an exaggerated increase of extracellular 5-HT in the hippocampus and frontal cortex (Knobelman et al. 2001; Mayorga et al. 2001; Trillat et al. 1997), similar to the augmenting effect of the 5-HT_{1B} receptor antagonist GR 127935 when combined with fluoxetine (Knobelman et al. 2001). This larger neurochemical response was accompanied by increased sensitivity to the behavioral effect of fluoxetine in the TST (Mayorga et al. 2001), supporting an important role for terminal 5-HT_{1B} autoreceptors in antidepressant treatment. 5-HT_{1B} KO females exhibited a decrease in baseline immobility in the TST and FST compared to KO males and WT mice because of a constitutive disinhibition of 5-HT release, resulting in higher levels of extracellular 5-HT (Jones and Lucki 2005a, b). This explains why the depletion of 5-HT increased TST immobility only in female 5-HT_{1B} receptor KO mice, and may be related to sex-related differences in the effects of stress and AD treatment.

5-HT_{2A} receptor—5-HT_{2A} receptors (Table 1) are densely expressed in the cerebral, piriform, and entorhinal cortices, claustrum, olfactory bulb, anterior olfactory nucleus, and a number of brainstem nuclei (Hannon and Hoyer 2008). Intermediate levels of expression have been measured in the limbic system and in the basal ganglia. 5-HT_{2A} receptors couple via $G_{q/11}$ to the IP3/PKC/calcium pathway. 5-HT_{2A} receptor agonists are associated with the behavioral effects of hallucinogenic drugs, such as LSD and antipsychotic drugs used to treat schizophrenia (Stockmeier et al. 1993). Chronic administration of different types of ADs to rodents, including SSRIs, causes reduction in the density of 5-HT_{2A} receptors in the frontal cortex (Peroutka and Snyder 1980), a mechanism that may participate in their therapeutic effects. Increased 5-HT_{2A} receptor density has been reported in depressed patients (Maes and Meltzer 1995; Meyer et al. 2003; Shelton et al. 2009) and a polymorphic allele for 5-HT_{2A} receptors associated with rates of recovery for SSRIs in treating depression (McMahon et al. 2006). Several atypical antipsychotic drugs have been used clinically for treating bipolar depression or in combination with SSRIs to augment their clinical efficacy (Nelson and Papakostas 2009; Philip et al. 2008).

Selective 5-HT_{2A} receptor antagonists have been reported to produce AD-like effects (Table 2) in the FST (Albinsson et al. 1994; Patel et al. 2004) and chronic administration of the 5-HT_{2A} antagonist BIP-1 produced AD-like effects in the OB model using the FST, sucrose

preference test, social interaction test, and open-field exploration as behavioral responses (Pandey et al. 2010). Co-administration of 5-HT_{2A} receptor antagonists also augmented the antidepressant-like behavioral effects of SSRIs measured using operant behavior (Marek et al. 2003; Marek et al. 2005). The mechanism for this interaction may be a further increase in extracellular 5-HT levels produced when SSRIs are given with 5-HT_{2A} receptor antagonists (Boothman et al. 2006).

5-HT_{2A} receptor antagonists may also produce antide-pressant-like effects by regulating the release of other neurotransmitters. For example, antagonists at 5-HT_{2A} receptors inhibited dopamine release in the prefrontal cortex (Pehek et al. 2006) whereas agonists enhanced dopaminergic activity (Bortolozzi et al. 2005). Treatment with the 5-$HT_{2A/2C}$ receptor agonist DOI caused an increase in glutamate release in cortex that was blocked by pretreatment with a selective 5-HT_{2A} receptor antagonist (Scruggs et al. 2003). Blockade of 5-HT_{2A} receptors by atypical antipsychotics also reversed the suppressant action of SSRIs on neuronal firing in the locus coeruleus, a possible mediator of their therapeutic benefit in resistant depression (Blier and Szabo 2005; Dremencov et al. 2007). Coadministering SSRIs with atypical antipsychotic drugs has gained clinical importance because of interest in their augmenting ADs and treating bipolar disorder. The specific mechanisms associated with the behavioral effects produced by the drug combinations remain to be determined.

5-HT_{2c} receptor—The 5-HT_{2C} receptor (Table 1) was identified initially in the choroid plexus from receptor autoradiography studies, but subsequently was found to be expressed in the hippocampus, amygdala, anterior olfactory and endopiriform nuclei, cingulate and piriform cortex, thalamic nuclei, and the substantia nigra (Hannon and Hoyer 2008). 5-HT_{2C} receptors couple preferentially to Gq/11 to increase inositol phosphates and cytosolic calcium concentrations. They are associated with the effects of a number of drug classes in psychopharmacology, including hallucinogens, psychostimulants, antipsychotics, and antidepressant drugs. However, understanding the pharmacology associated with 5-HT_{2C} receptors is complex due to the receptor being linked with multiple cellular signaling responses, unusual regulation allowing down-regulation by chronic administration of agonists or antagonists and mRNA editing allowing for post-translational processing (Berg et al. 2008). In addition, 5-HT_{2C} receptors have constitutive activity so that inverse agonists decrease baseline signaling. Some antidepressants, including mianserin, mirtazepine, trazodone, and nefazodone, have high affinity at 5-HT_{2C} receptors, although SSRIs (sertraline, paroxetine, citalopram), with the exception of fluoxetine, do not generally show affinity for the receptor (Sanchez and Hyttel 1999). Some atypical antipsychotic drugs also block 5-HT_{2C} receptors, increase extracellular NE and DA levels and augment the increase of extracellular 5-HT levels by SSRIs (Cremers et al. 2007; Dremencov et al. 2005). These neuropharmacological effects may allow these drugs to augment the clinical effects of SSRIs in treatment-resistant patients (Nelson and Papakostas 2009; Wood et al. 2006).

A number of 5-HT_{2C} receptor agonists, Ro-60-0175, Ro-60-0332, WAY 161503, and WAY 163909, have been reported to produce AD-like effects (Table 2) in the modified rat FST, resident-intruder social stress model, and OB models of depression (Cryan and Lucki 2000b; Rosenzweig-Lipson et al. 2007). In addition, the selective 5-HT_{2C} receptor antagonist SB206533 blocked the behavioral effects of fluoxetine in the rat FST (Cryan and Lucki 2000b). Although the 5-HT_{2C} receptor antagonist mianserin produced AD-like effects in the FST, this was likely due to alpha2 receptor blockade (Cryan and Lucki 2000b). In the mouse FST, the 5-HT_{2C} receptor agonist Ro 60-0175 synergized with sub-active doses of imipramine, paroxetine, citalopram, and fluvoxamine but antagonized active doses of paroxetine and fluoxetine at higher doses (Clenet et al. 2001). 5-HT_{2C} KO mice demonstrate an anxiolytic phenotype with a blunted CRF response to stress, but their phenotype in tests for AD effects was not reported (Heisler et al. 2007). That 5-HT_{2C} KO mice are

hyperresponsive to the effects of repeated stress would seem to support the findings that agonists produce AD-like effects (Chou-Green et al. 2003).

There is also a substantial rationale for 5-HT_{2C} receptor antagonists to produce antidepressant effects. Several established ADs, such as mianserin and mirtazepine, are potent 5-HT_{2C} receptor antagonists. Agomelatine is an agonist of melatonin receptors (MT1 and MT2) and a 5-HT_{2C} receptor antagonist that has recent been introduced as a novel antidepressant involving nonmonoaminergic receptors (de Bodinat et al. 2010). The effects of melatonin receptors are thought to regulate circadian rhythms disrupted by chronic stress and agomelatine has shown antidepressant-like activity in a number of rodent tests, including the FST, learned helplessness, olfactory bulbectomy and chronic mild stress models. S32006 is a novel 5-HT_{2C} receptor antagonist that decreased immobility in the rat FST. Chronic administration of the 5-HT_{2C} receptor antagonist S32006 also diminished anhedonia in the CMS procedure and increased cell proliferation and the expression of BDNF in the rat dentate gyrus (Dekeyne et al. 2008).

It may seem paradoxical that 5-HT_{2C} receptor agonists and antagonists produce similar kinds of behavioral outcomes from opposing pharmacological profiles. The paradox is resolved if 5-HT_{2C} receptor agonists and antagonists produce similar behavioral effects by diverse mechanisms (Fig. 1). For example, stimulation of 5-HT_{2C} receptors may be an important component of the global stimulation of postsynaptic 5-HT receptors by SSRIs that produces antidepressant effects. However, 5-HT_{2C} receptor antagonists may also produce similar AD-like effects by facilitating the release of other neurotransmitters, such as norepinephrine and dopamine (Dekeyne et al. 2008; Dremencov et al. 2006; Esposito 2006). Except for the modified rat FST (Cryan et al. 2005c), few tests distinguish the effects of antidepressants that facilitate norepinephrine or dopamine from 5-HT transmission unless employing pharmacological depletions. The existence of complementary substrates associated with the behavioral effects of 5-HT_{2C} receptor agonists and antagonists, respectively, could be confirmed by subsequent mechanistic studies.

5-HT_3 receptor—5-HT_3 receptors (Table 1) belong to the superfamily of ligand-gated ion channels and are the same as the historical M receptor characterized by Gaddum and Picarelli (1957). These receptors trigger rapid depolarization of neurons by opening non-selective cation channels. Radioligand autoradiography has mapped the distribution of 5-HT_3 receptors, with the highest levels located in dorsal vagal complex where receptor antagonists likely produce their antiemetic effects (Hannon and Hoyer 2008). Other areas of 5-HT_3 receptor expression in brain include the hippocampus, amygdala, and cortex. 5-HT_3 receptors can mediate the indirect inhibition of excitatory pyramidal neurons by activating GABA interneurons.

The 5-HT_3 receptor has been identified as a target for potential antidepressant drugs (Rakjumar and Mahesh 2010). Antagonists at 5-HT_3 receptors (tropisetron, ondansetron) produced antidepressant-like effects (Table 2) in a number of tests and models in mice and rats (Mahesh et al. 2007; Martin et al. 1992). Additionally, cotreatment with ondansetron augmented the effects of subthreshold doses of SSRIs in the mouse FST (Ramamoorthy et al. 2008; Redrobe and Bourin 1997). On the other hand, the 5-HT_3 receptor agonist 1-(*m*-Chlorophenyl)-biguanide attenuated the effects of antidepressant compounds in the rat FST (Nakagawa et al. 1998). The effects of 5-HT_3 receptor antagonists may mimic a direct receptor interaction of some clinically effective antidepressants, including fluoxetine, that have been reported to functionally block 5-HT_3 receptors (Eisensamer et al. 2003).

Interestingly, female 5-HT_3 receptor KO mice show increased immobility in the FST compared to WT controls suggesting that sex-specific regulation of the receptor may be

important for the development of depression-like behaviors (Bhatnagar et al. 2004; Bravo and Maswood 2006; Martin et al. 1992). The 5-HT_3 receptor antagonist tropisetron reduced immobility and increased swimming in the modified FST in female rats, but its effects were dependent on the stage of the estrous cycle (Bravo and Maswood 2006).

5-HT_4 receptor—The 5-HT_4 receptor (Table 1) is distributed widely in limbic regions of the brain, being densely located in the nigrostriatal and mesolimbic systems and also the septum, hippocampus and amygdala (Hannon and Hoyer 2008). Although a number of 5-HT_4 receptor splice variants have been reported, all have overlapping pharmacological profiles and are positively coupled to adenylate cyclase. 5-HT_4 receptor agonists have been studied by a number of laboratories for facilitation of memory which may be associated with their ability to regulate acetylcholine release (Meneses 2007).

The 5-HT_4 receptor agonist RS 67333 was reported to produce behavioral effects (Table 2) in rats in a number of tests used to measure the acute (FST) or chronic effects (OB and CMS) of antidepressant drugs. Most interestingly, only a 3-day treatment regimen with the 5-HT_4 receptor agonist RS 67333 was required to desensitize 5-HT_{1A} autoreceptors, increase CREB phosphorylation and neurogenesis in the hippocampus, decrease hyperlocomotion in the OB model, and normalize sucrose consumption in the CMS model (Lucas et al. 2007), suggesting more rapid onset of a number of adaptations usually requiring chronic AD treatment. Combining RS 67333 with fluvoxamine, citalopram, or fluoxetine produced larger behavioral effects in the FST than any of the compounds given alone (Lucas et al. 2010). When combined with evidence for a more rapid onset of antidepressant effects and cognitive facilitating effects, 5-HT_4 receptor agonists may produce a unique pattern of antidepressant response. The behavioral effects of RS 67333 in the FST and TST were not present in p11 KO mice suggesting that this protein plays an integral role in 5-HT_4 receptor-mediated AD-like effects, as it does for 5-HT_{1B} receptor-mediated effects (Warner-Schmidt et al. 2009).

Pharmacological blockade or genetic deletion of the 5-HT_4 receptor has also been reported to exert anxiolytic effects in some behavioral tests (Compan et al. 2004; Conductier et al. 2006; Smriga and Torii 2003). However, the 5-HT_4 receptor antagonist SB 204070A produced no effects when administered alone and did not alter the behavioral effects of fluoxetine in the modified rat FST suggesting that activation of the 5-HT_4 receptor is not required for the behavioral effects of fluoxetine in the test (Cryan and Lucki 2000a).

5-HT_6 receptor—The 5-HT_6 receptor (Table 1) is located principally in the brain where it is coupled to the stimulation of adenylate cyclase activity (Hannon and Hoyer 2008). Autoradiography studies have shown that the highest density of 5-HT_6 receptors are located in the striatum, nucleus accumbens, olfactory tubercle, and cortex with moderate expression levels in the amygdala, hypothalamus, thalamus, cerebellum, and hippocampus. There is evidence that 5-HT_6 receptors regulate the release of a number of neurotransmitters, such as acetylcholine, norepinephrine, GABA and dopamine, which could provide an additional mechanism for their effectiveness in treating psychiatric disorders. A number of antipsychotic drugs (clozapine, olanzapine, quetiapine) and ADs (clomipramine, amitriptyline, doxepin) act as 5-HT_6 receptor antagonists, but without selectivity for this receptor. Selective 5-HT_6 receptor agonists and antagonists have both been reported to produce cognitive enhancing effects in rodents (Fone 2008), a beneficial effect that could significantly improve the clinical effects of SSRIs.

Research has shown that antidepressant and anxiolytic effects are produced by 5-HT_6 receptor agonists (Table 2) in a number of tests in mice and rats. The 5-HT_6 receptor agonist EMDT reduced immobility in the mouse TST, whereas the 5-HT_6 antagonist SB271046

prevented the antidepressant effects of EMDT and fluoxetine (Svenningsson et al. 2007). Our group recently found that the selective 5-HT_6 receptor agonists WAY-181187 and WAY-208466 produce AD-like effects in the modified rat FST and anxiolytic-like effects in the defensive burying and NIH models after acute treatment (Carr et al. 2010). Acute efficacy of 5-HT_6 receptor agonists in the NIH model was especially intriguing because SSRIs produced anxiolytic effects in this test only after chronic treatment (Bechtholt et al. 2008). Although chronic administration of WAY-181187 persistently altered scheduled-induced polydipsia (Schechter et al. 2008), a putative model of compulsive behavior, 5-HT_6 receptor agonists have not been examined on antidepressant tests after chronic administration.

Just as for their effects in tests of cognition (Fone 2008), both 5-HT_6 receptor agonists and antagonists have been reported to produce similar effects in animal tests for AD activity (Wesolowska 2010; Wesolowska and Nikiforuk 2007). 5-HT_6 receptor antagonists also augmented the antiimmobility effects of antidepressants in the FST (Wesolowska and Nikiforuk 2008). The likely explanation for this paradox is that 5-HT_6 receptor agonists and antagonist produce diverse neurochemical effects that result in similar behavioral outcomes, similar to the scheme proposed for 5-HT_{2C} receptor agonists and antagonists (Fig. 1). The activation of 5-HT_6 receptors would likely produce behavioral effects similar to the effects of SSRIs through the global stimulation of postsynaptic 5-HT receptors. 5-HT_6 receptor antagonists may also produce AD-like responses by facilitating the release of other neurotransmitters, e.g., norepinephrine or dopamine (Wesolowska 2007). The AD-like and anxiolytic-like effects of the 5-HT_6 antagonist SB-399885 persisted after 5-HT depletion, suggesting that the effects of this compound were not dependent on endogenous serotonergic neurotransmission (Wesolowska 2007).

5-HT_7 receptor—The 5-HT_7 receptor (Table 1) was identified through a homology cloning strategy and modulates positive cAMP formation via G_s. The receptor is located in highest density in the medial thalamic nuclei, limbic, and cortical regions suggesting a role in sensory and affective processes (Hannon and Hoyer 2008). The selective expression of 5-HT_7 receptors in the suprachiasmatic nucleus is consistent with a role in sleep or circadian rhythmic activity. Changes in temperature regulation have been used to identify 5-HT_7 receptor agonists and antagonists.

Studies have shown that reducing the function of 5-HT_7 receptors may produce AD-like behavioral effects. Testing in the FST and TST (Table 2) has shown AD-like effects in rodents following the genetic deletion of 5-HT_7 receptors or administration of 5-HT_7 receptor antagonists (Guscott et al. 2005; Hedlund et al. 2005; Wesolowska et al. 2006). Although 5-HT_7 receptor blockade is unlikely to be involved in the effects of SSRIs, research suggests that 5-HT_7 receptor antagonists have potential as adjunctive antidepressant treatments. A recent study showed that 5-HT_7 receptor antagonists increased the effects of citalopram on the TST (mice) and REM sleep (rats; Bonaventure et al. 2007). The antipsychotic amisulpride produced AD-like effects clinically (Kim et al. 2007) and recent preclinical studies showed that these effects may be due to 5-HT_7 receptor antagonist properties of the compound (Abbas et al. 2009). The mechanism of action of 5-HT_7 receptor antagonists is not known.

5-HT transporter KO mice

The involvement of the 5-HT transporter (SERT) in clinical depression and anxiety has received enormous attention from discovery of the significance of SERT polymorphisms on human behavior (Murphy et al. 2008). The absence of normal responses to SSRIs in SERT KO mice demonstrates that actions on SERT are a critical principle mechanism of action of

members of this class of ADs (Fox et al. 2007). SERT KO mice also demonstrated reduced temperature, locomotor, and electrophysiological responses to 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} receptor agonists.

The behavior of SERT KO mice on tests for AD effects is dependent on the background strain. With a C57/BL6 background, there were no differences in baseline behavior (Table 2) in the FST or TST between KO and wild-type (WT) mice (Holmes et al. 2002). On the C57/BL6 background, fluoxetine had no effect on behavior in the TST while ADs not dependent on 5-HT to exert their effects (desipramine and imipramine) were still effective (Holmes et al. 2002). In contrast, on the 129S6 background, SERT KO mice exhibited an increase in immobility in the FST (prodepressive) and a decrease in immobility in the TST (AD-like) response at baseline compared to WT controls (Holmes et al. 2002; Lira et al. 2003). Showing that a similar life-long pro-depressive sensitivity in adult mice can be produced by early postnatal exposure to SSRIs, the stress-sensitive phenotype was thought to arise from the stimulation of corticolimbic circuits in early life (Ansorge et al. 2008). It is unclear why deletion of the SERT protein did not always produce the same baseline behavioral effects as pharmacological blockade of the protein with SSRIs. Some possible explanations include the involvement of developmental alterations of 5-HT receptor function and/or changes in the endogenous release of 5-HT following drug treatment (Fabre et al. 2000; Gobbi et al. 2001).

Conclusion

Behavioral and neuropharmacology studies have attempted to identify the 5-HT receptor subtypes associated with the therapeutic effects of SSRIs. Identifying the role of different 5-HT receptors in the antidepressant responses of SSRIs is an important step in understanding their mechanism of action in treating depression and anxiety and for developing more effective ADs with fewer side effects.

Since the discovery of the SSRIs as a major class of psychotherapeutic drugs, a large amount of research has attempted to elucidate the role of the 5-HT system in genetic and molecular mechanisms underlying the pathology and treatment of depression. Genes for 5-HT synthesizing enzymes and multiple receptors may constitute a family of risk factors that can contribute to the pathology of depression (Jans et al. 2007). Physiological dysfunction at any of a series of critical 5-HT targets, either early or late in life, can contribute to the development of psychiatric disorders. The developmental role of 5-HT is emphasized by deletion of 5-HT_{1A} receptors or the SERT (Ansorge et al. 2008; Gross et al. 2002) although few studies have recapitulated a predisposition for depressive behavior by interfering with 5-HT (Beaulieu et al. 2008). The further development of methods that model the contribution of the components of the 5-HT system to behavioral pathology will improve our ability to invent better treatment for psychiatric disorders.

This review has considered the evidence for how different 5-HT receptor subtypes participate in the behavioral effects of SSRIs on tests for depressive behavior as models of the psychotherapeutic treatment response. SSRIs increase extracellular 5-HT levels at all postsynaptic 5-HT receptors. Instead of a single 5-HT receptor, research studies point to the participation of a family of pharmacological effects involving multiple 5-HT receptors and neural mechanisms as being responsible for the antidepressant effects of SSRIs. Direct agonists at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_4, and 5-HT_6 receptors best recapitulate the behavioral effects of SSRIs on tests for AD-like behavior and depression models. In contrast, SSRIs would trigger these multiple mechanisms simultaneously. The receptor agonists would evoke specific mechanism individually and, until appropriate compounds are tested, it is unclear whether any of these individual selective 5-HT receptor agonists could

reproduce the entire spectrum of clinical effects of SSRIs or produce fewer side effects. More interesting for clinical development, however, is whether some direct agonists may have additional clinical benefits over the use of SSRIs. For example, 5-HT_4 and 5-HT_6 receptor agonists increased performance on cognitive tests in animal models. If this effect translated to clinical treatment, these drugs could improve therapeutic benefits over SSRIs. But just as multiple 5-HT receptors are involved in the therapeutic effects of SSRIs, genetic polymorphisms for any of the 5-HT receptor subtypes may constitute risk factors that contribute to the development of depression or limit the therapeutic benefits of SSRIs. Several 5-HT receptors (5-HT_{1E}, 5-HT_{1F}, 5-HT_{2B}, 5-HT_5 receptors) were not discussed in this review because their role in antidepressant responses has not been elucidated.

This review also considered that several antagonists of a number of 5-HT receptor subtypes also produced AD-like behavioral effects indicating that complementary behavioral effects can be triggered by blocking 5-HT receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7). These effects may be obtained by administration of the antagonists alone or may require combination with other therapeutic compounds to augment their clinical effects. For example, blockade of 5-HT_{2A} and 5-HT_{2C} receptors is likely involved in the antidepressant effects of mianserin and mirtazepine. Blockade of 5-HT_{2A} and 5-HT_{2C} receptors are also important when considering some of the new combinations of drugs being used to treat depression, such as combining SSRIs with atypical antipsychotics.

The best evidence supports SSRIs producing their behavioral effects relevant to depression and anxiety by enhancing 5-HT transmission, although it is possible for SSRIs to produce behavioral responses through non-5-HT mechanisms. Individual 5-HT receptor subtypes are also known to regulate the release of other neurotransmitters. Combining a SSRI with a 5-HT receptor agonist or antagonist that modifies 5-HT transmission can produce a new molecule that may have greater benefit in treating depression. For example, the prospective antidepressant vilazodone produces increases in extracellular 5-HT levels that are larger than those produced by fluoxetine by combining a 5-HT_{1A} receptor partial agonist with a SSRI (Dawson and Watson 2009; Page et al. 2002). The benefit of producing a larger increase of 5-HT levels remains unclear. It also remains to be seen if similar molecules with beneficial effects can be obtained by combining SSRIs with 5-HT_{1B} (or 5-HT_{1D} in humans) receptor antagonists (Dawson et al. 2006), with 5-HT_{2C} receptor antagonists (Cremers et al. 2007), or with α-adrenergic agonists that stimulate 5-HT neural activity and release (Beyer et al. 2006). The novel antidepressant agomelatine exploits combining the effects of 5-HT_{2C} receptor blockade with stimulating melatonin receptors (de Bodinat et al. 2010). Drug development strategies may combine SSRIs with other prospective antidepressant targets to exploit additional therapeutic benefits from a broader base of pharmacological effects (Millan 2006). One thing that is unclear, however, is how the improved benefit to therapeutic treatment may appear in preclinical tests of antidepressant activity and be differentiated from the behavioral effects of SSRIs.

There are further challenges for understanding the mechanisms underlying the behavioral effects for SSRIs that may be associated with their clinical effects in depression and anxiety. Amajor challenge in the field is identifying the neural circuitry associated with the AD-like effects of SSRIs and integrating this knowledge with clinical studies using neuroimaging technology. The circuitry for the AD-like effects of different 5-HT receptor subtypes may lie distinctly in particular sites or involve overlapping components governed by distributed regions in the brain. Multiple systems may participate in different types of AD responses. Another important medical need is understanding the genetic, environmental, or pharmacological factors leading to treatment resistance. As SSRIs are the current leading modality for treating depression, further research into factors contributing to resistance to SSRI treatment is needed to produce new ADs that are effective through complementary

mechanisms of action. Along these directions, future research with preclinical models will guide the development of the next generation of antidepressant drugs.

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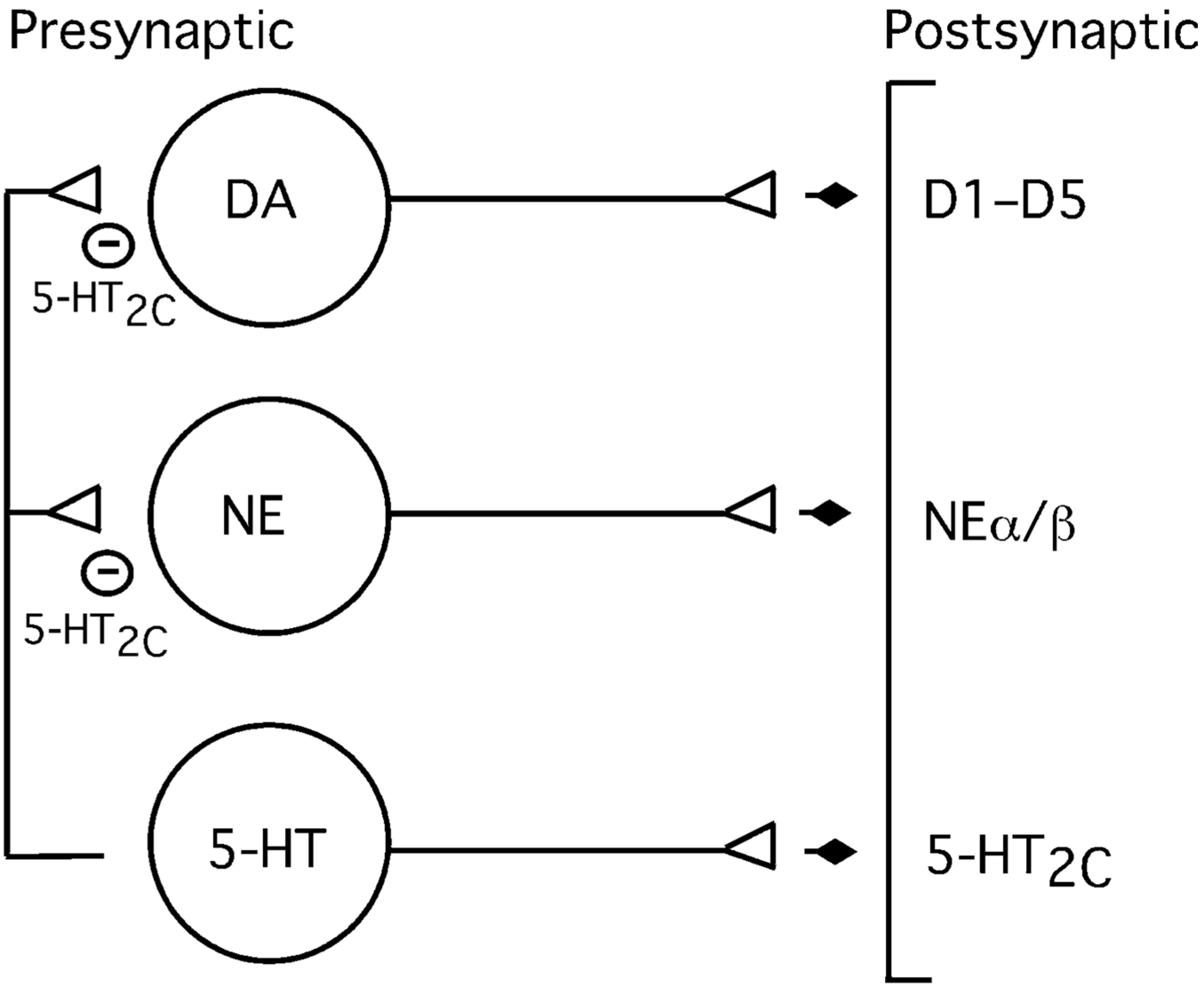

Fig. 1.

Schematic representing two ways that 5-HT_{2C} receptors may be involved in producing the behavioral effects of antidepressant drugs. 5-HT_{2C} receptor agonists may produce antidepressant-like behavioral effects by directing stimulating 5-HT_{2C} receptors. This would be a subset of the effects produced by the global stimulation of postsynaptic 5-HT receptors with SSRIs. In contrast, 5-HT_{2C} receptor antagonists may produce antidepressant-like behavioral effects by increasing the release of NE and DA in terminal regions such as the nucleus accumbens by blocking the tonic inhibition of DA and NE release exerted by 5-HT_{2C} receptors

Table 1

Signaling pathways, location, and pharmacology of 5-HT receptor subtypes

Receptor	Major signaling pathway	Neuronal location	Regional localization	Agonists	Antagonists
5-HT_{1A}	↓cAMP	Somatic autoreceptor/postsynaptic	Raphe nuclei/hippocampus, cortex	8-OH-DPAT, Buspirone	WAY 100635
5-HT_{1B}	↓cAMP	Terminal autoreceptor/postsynaptic	Striatum, nucleus accumbens, ventral tegmental area	Anpirtoline, CP 94253	SB 224289, GR 127935
5-HT_{2A}	IP_3	Postsynaptic	Frontal cortex	DOI	Ketanserin, M 100907
5-HT_{2C}	IP_3	Postsynaptic	Frontal cortex	m-CPP, R0 600175	Mesulergine, SB 200907
5-HT_3	Ion channel	Postsynaptic	Cortex, amygdala	mCPBG, 2-CH_3-5-HT	Ondansetron, Tropisetron
5-HT_4	↑cAMP	Postsynaptic	Striatum, nucleus accumbens, cortex	BIMU-8, RS 67333, Cisapride	GR 113808, SB 204070
5-HT_6	↑cAMP	Postsynaptic	Hippocampus, cortex	EMDT, WAY 181187, WAY 208466	SB 399885
5-HT_7	↑cAMP	Postsynaptic	Suprachiasmatic nucleus, cortex	8-OH-DPAT	Amisulpiride, SB 269970

Table 2

5-HT receptors and rodent behavioral tests of depression-related behaviors

Receptor KO	KO	Agonists	Antagonists	Behavior Test	References
5-HT$_{1A}$		AD-like		FST	Cervo et al. 1988
		AD-like		FST	Kostowski et al. 1992
		AD-like		FST	Singh and Lucki 1993
		AD-like		FST	Detke et al. 1995a, b
		AD-like		NIH	Bodnoff et al. 1989
		AD-like		OB model	Cryan et al. 1997
		AD-like		LH model	MacSweeney et al. 1998
		AD-like		LH model	Tordera et al. 2002
		AD-like		CMS model	Przegalinski et al. 1995
		AD-like		CMS model	Tordera et al. 2002
			Augmented fluoxetine	DRL 72 s	Cousins and Seiden 2000
			Augmented duloxetine	FST	Millan et al. 1998
			Augmented and blocked fluoxetine	FST	Cryan et al. 2005c
	AD-like at baseline Blocked fluoxetine			TST	Mayorga et al. 2001
	AD-like at baseline			TST	Jones and Lucki 2005a, b
	Blocked fluoxetine			NIH, neurogenesis	Santarelli et al. 2003
	Blocked fluoxetine			FST, NIH, neurogenesis	Holick et al. 2008
	Augmented fluoxetine increase of 5-HT levels		Augmented fluoxetine increase of 5-HT levels	Microdialysis	Knobelman et al. 2001
5-HT$_{1B}$		AD-like		FST	Tatarczynska et al. 2005
		AD-like	Blocked SSRIs	FST	Chenu et al. 2008
			Augmented paroxetine	FST	Tatarczynska et al. 2002
			AD-like	FST	Dawson et al. 2006
	AD-like (females)			FST, TST	Jones and Lucki 2005a, b
	Augmented fluoxetine			TST	Mayorga et al. 2001
	Augmented SSRIs increase of 5-HT levels		Augmented SSRIs increase of 5-HT levels		Trillat et al. 1997Knobelman et al. 2001
5-HT$_{2A}$			AD-like	FST	Albinsson et al. 1994
			AD-like	FST	Patel et al. 2004

Receptor KO	KO	Agonists	Antagonists	Behavior Test	References
			AD-like Augmented SSRIs	DRL 72 s	Marek et al. 2005
			AD-like	OB model	Pandey et al. 2010
			Augmented SSRIs on 5-HT levels		Boothman et al. 2006
5-HT$_{2C}$		AD-like	Blocked fluoxetine	FST	Cryan and Lucki 2000b
		AD-like		FST, OB model	Rosenzweig-Lipson et al. 2007
		Augment SSRIs on behavior		FST	Clenet et al. 2001
			AD-like	FST, CMS model	Dekeyne et al. 2008
5-HT$_3$			AD-like	LH model	Martin et al. 1992
			AD-like	FST, TST, OB model	Mahesh et al. 2007
			Augmented SSRIs	FST	Redrobe and Bourin 1997
			AD-like Augmented SSRIs	FST, TST, OB model	Ramamoorthy et al. 2008
		Blocks AD effects	AD-like	FST	Nakagawa et al. 1998
	Prodepressive (females)			FST	Bhatnagar et al. 2004
			AD-like (females)	FST	Bravo and Maswood 2006
5-HT$_4$		AD-like	Augmented SSRIs	FST, OB model, CMS model	Lucas et al. 2007
5-HT$_6$		AD-like		TST	Svenningson et al. 2007
		AD-like		FST, NIH	Carr et al. 2010
			AD-like	FST, TST	Wesolowska and Nikiforuk 2007
			Augmented SSRIs	FST	Wesolowska and Nikiforuk 2008
5-HT$_7$	AD-like		AD-like	FST	Guscott et al. 2005
	AD-like		AD-like	FST, TST	Hedlund et al. 2005
			AD-like	FST, TST	Wesolowska et al. 2006
			Augmented SSRIs	FST	Wesolowska 2007
			AD-like Augmented SSRIs on behavior and 5-HT levels	TST, Microdialysis	Bonaventure et al. 2007
SERT	C57BL/6: No effect on baseline; Blocked fluoxetine in the TST			TST, FST	Holmes et al. 2002
	129S6: Increased immobility in FST; Decreased immobility in TST			TST, FST	Holmes et al. 2002
	129S6/SvEv: Increased immobility in FST; Decreased immobility in TST; Increased NIH latency			TST, FST, NIH	Lira et al. 2003