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Therapeutic Potential of 5-HT$_{2C}$ Receptor Agonists for Addictive Disorders

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ABSTRACT: The neurotransmitter 5-hydroxytryptamine (5-HT; serotonin) has long been associated with the control of a variety of motivated behaviors, including feeding. Much of the evidence linking 5-HT and feeding behavior was obtained from studies of the effects of the 5-HT releaser (dex)fenfluramine in laboratory animals and humans. Recently, the selective 5-HT$_{2C}$ receptor agonist lorcaserin received FDA approval for the treatment of obesity. This review examines evidence to support the use of selective 5-HT$_{2C}$ receptor agonists as treatments for conditions beyond obesity, including substance abuse (particularly nicotine, psychostimulant, and alcohol dependence), obsessive compulsive, and excessive gambling disorder. Following a brief survey of the early literature supporting a role for 5-HT in modulating food and drug reinforcement, we propose that intrinsic differences between SSRI and serotonin releasers may have underestimated the value of serotonin-based pharmacotherapeutics to treat clinical forms of addictive behavior beyond obesity. We then highlight the critical involvement of the 5-HT$_{2C}$ receptor in mediating the effect of (dex)fenfluramine on feeding and body weight gain and the evidence that 5-HT$_{2C}$ receptor agonists reduce measures of drug reward and impulsivity. A recent report of lorcaserin efficacy in a smoking cessation trial further strengthens the idea that 5-HT$_{2C}$ receptor agonists may have potential as a treatment for addiction. This review was prepared as a contribution to the proceedings of the 11th International Society for Serotonin Research Meeting held in Hermanus, South Africa, July 9−12, 2014.

KEYWORDS: *Serotonin, 5-HT$_{2C}$ receptor, impulsivity, addiction, obesity, lorcaserin, nicotine dependence*

OBESITY AND SUBSTANCE ABUSE CA. 1987: SEPARATE RESEARCH QUESTIONS

At the time of the inaugural Serotonin Club meeting in 1987, research into the mechanisms and treatment of obesity was distinct from research into the causes and treatment of addiction. Obesity was viewed predominantly as a metabolic condition, whereas addiction was seen as a central nervous system (CNS) disorder, involving drug taking and, in some cases, signs of physical dependence such as drug tolerance and withdrawal symptoms.[1] A role for serotonin in modulating food intake and body weight gain was well-established, being supported by the results of many studies in laboratory animals and in humans.[2−4] In parallel, a smaller body of work involving the use of nonselective drugs such as fenfluramine, tryptophan, and selective serotonin reuptake inhibitors (SSRIs) as well as serotonin neurone lesioning approaches suggested that serotonin could modulate the effects of drugs of abuse, particularly the psychostimulants cocaine and amphetamine, as well as alcohol.[5−12] To a large extent, it seems that these two areas of serotonin research developed somewhat independently with little cross-talk.

On the basis of this preclinical evidence, serotonergic drugs (primarily SSRIs) were investigated in clinical trials for substance/alcohol abuse. However, outcomes were inconsistent, with none of these drugs being approved for treatment of substance/alcohol abuse (see ref 13 for a comprehensive review). Clinical trials with SSRIs for alcohol abuse were largely unsuccessful, with only very modest decreases relative to placebo reported in end points such as urge to drink and number of drinks consumed.[14−17] Mostly negative outcomes were also reported in smoking cessation trials of multiple SSRIs, at least in terms of promoting abstinence (reviewed in ref 18). A modest effect of the SSRI citalopram[19] on measures of cocaine abstinence in dependent subjects was reported, although this has not been replicated with other SSRI's including fluoxetine.[20−22] Greater success was realized for the use of serotonergic drugs in individuals wishing to lose weight, culminating in the approval of (dex)fenfluramine and its combination with phentermine (phen-fen) for the treatment of obesity.[23−26]

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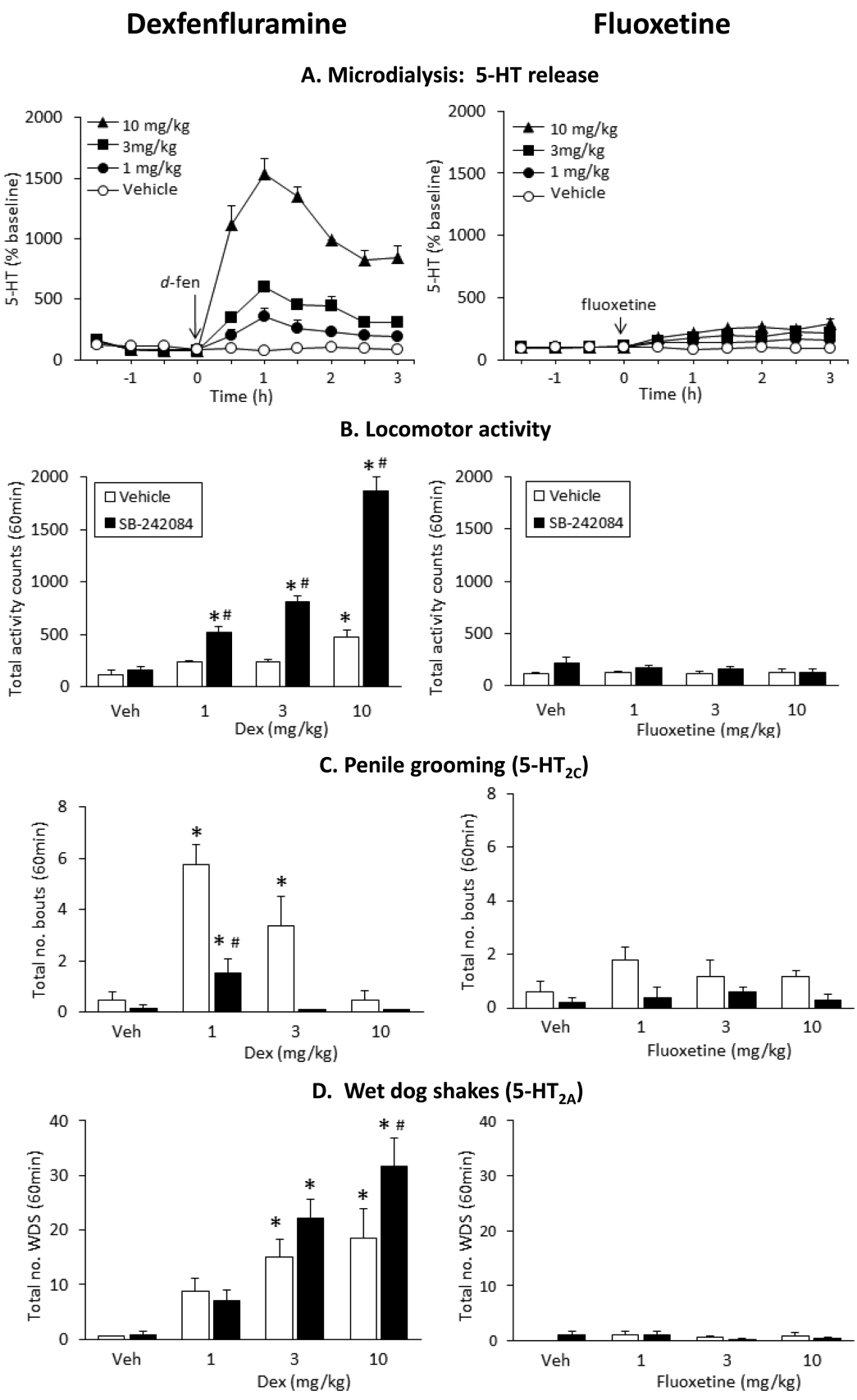

Figure 1. Comparison between a 5-HT releaser (dexfenfluramine) and SSRI (fluoxetine) on (A) extracellular 5-HT release sampled from rat hypothalamus, (B) locomotor activity, (C) penile grooming (a 5-HT_{2C} receptor-mediated behavior), and (D) wet dog shakes (WDS) (a 5-HT_{2A} receptor-mediated response). All figures are drawn to the same scale to highlight differences between the magnitude of the change produced by each drug. Note that dexfenfluramine (1−10 mg/kg) induces penile grooming at low doses (1−3 mg/kg) and WDS and hyperlocomotion at higher doses (3−10 mg/kg). Blockade of 5-HT_{2C} receptors with SB-242084 (0.5 mg/kg) inhibits penile grooming and intensifies the WDS and particularly the

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Figure 1. continued

motor response. These data demonstrate an intensification of 5-HT_{2A} receptor mediated behaviours by dexfenfluramine (1−10 mg/kg) when 5-HT_{2C} receptors are simultaneously blocked. In contrast, fluoxetine produces a much weaker induction of penile grooming and little or no WDS or hyperactivity, and the expression of all of these effects is unaffected by SB-242084 pretreatment. Consequently, there is little evidence for 5-HT_{2C} receptor activation following fluoxetine (1−10 mg/kg) pretreatment under these conditions. * $P < 0.05$ vs corresponding vehicle control; # $P < 0.05$ vs corresponding dexfenfluramine dose. Data in (A) were adapted with permission from ref 35. Copyright 2002 Elsevier. Dexfenfluramine data from (B−D) were reprinted with permission from ref 39. Copyright 2001 John Wiley & Sons. Fluoxetine data from (B−D) are previously unpublished.

This apparent difference in the effects of serotonergic agents on measures of obesity and feeding compared to drug abuse may imply that 5-HT systems play a more prominent role in modulating food consumption and body mass compared to drug seeking behaviors. However, an alternative explanation for the apparent greater success of serotonin-based therapies for obesity compared to addiction may relate to the drug class used to treat these disorders. Thus, SSRIs were predominantly featured in clinical investigations in substance abusers, whereas (dex)fenfluramine was the primary serotonin-based drug investigated for the treatment of obesity. (Dex)fenfluramine was shown to reduce body weight in obese patients on the basis of large, well-powered clinical trials.[27,28] While there are occasional reports of the effects of (dex)fenfluramine in cocaine and alcohol users,[29−31] these were conducted in small study populations. Had (dex)fenfluramine been investigated under designs equivalent to those used in obesity trials, outcomes may have been more definitive compared to the unconvincing studies using SSRI-based treatments in substance abuse/alcohol trials. Furthermore, treatment with SSRIs has generally failed to produce sustained weight loss in extended obesity trials.[28,32,33] Despite the fact that SSRIs and (dex)fenfluramine both enhance serotonergic neurotransmission, the ineffectiveness of SSRIs is clearly a different outcome to that found following (dex)fenfluramine treatment. Conceivably, differences between the pharmacological properties of serotonin reuptake inhibition compared to serotonin release may underlie these apparent differences. The evidence supporting this possibility is reviewed in the following section, with a specific focus on potential differential engagement of 5-HT_{2C} receptor subtype activity following SSRI or (dex)fenfluramine treatment.

5-HT RELEASE VS REUPTAKE INHIBITION: DIFFERENTIAL ENGAGEMENT OF 5-HT_{2C} RECEPTOR-MEDIATED NEUROTRANSMISSION?

The sampling of extracellular fluids using *in vivo* microdialysis provides a direct way to study drug effects on synaptic efflux of a neurotransmitter. Comparisons of dexfenfluramine and fluoxetine using this technique have revealed a significant difference between the effects of reuptake inhibition and release on extracellular 5-HT levels.[34−36] For example, Tao et al.[35] compared the effects of fluoxetine and dexfenfluramine on extracellular 5-HT in the hypothalamus, with the latter increasing basal 5-HT 6−16-fold, compared to 3-fold following fluoxetine (Figure 1A). These differences in magnitude reflect differences in the way that fluoxetine and dexfenfluramine elevate 5-HT. The ability of SSRIs to increase extracellular 5-HT is dependent on neuronal activity (i.e., impulse dependent) and is subject to autoreceptor feedback inhibition. In contrast, (dex)fenfluramine increases extracellular 5-HT by disrupting vesicular storage and promoting nonexocytotic release that is independent of both of these regulatory factors.[36]

Such a difference in the extent of elevation of extracellular 5-HT levels might be predicted to differentially affect distinct 5-HT receptor populations, and this is indeed the case. Dexfenfluramine reliably induces behaviors that are characteristic of 5-HT_{2C} receptor activation, such as penile grooming.[37−39] SSRIs such as fluoxetine and citalopram do not evoke such responses to the same degree (e.g., Figure 1B−D). In contrast to dexfenfluramine,[40−42] the anorectic effects of SSRIs (fluoxetine, citalopram, sertraline) are not blocked by either selective or nonselective 5-HT_{2C} receptor antagonists.[43−47] Grignaschi et al.[47] speculated that this reflects an inability of SSRIs to sufficiently elevate extracellular 5-HT levels to activate 5-HT_{2C} receptors. This more restricted effect of SSRIs, compared to (dex)fenfluramine, on 5-HT levels could be due to differential activation of inhibitory somatodendritic 5-HT_{1A} autoreceptors in the raphe nuclei.[47] While some evidence supports a SSRI/5-HT_{2C} receptor interaction, for example, coadministration of a 5-HT_{2C} receptor antagonist augments the elevation in synaptic 5-HT levels induced by SSRIs.[48,49] Overall, however, the data suggest that SSRIs may not promote signaling through 5-HT_{2C} receptors to the same extent as that with (dex)fenfluramine. A second pharmacological factor that may further contribute to differences between the effects of (dex)fenfluramine and SSRIs is that the primary metabolite of (dex)fenfluramine, nor-(dex)fenfluramine, also has some modest agonist activity at the 5-HT_{2C} receptor.[50]

A further way in which SSRIs and fenfluramine may differentially alter serotonin neurotransmission relates to a functional interaction between 5-HT_{2A} and 5-HT_{2C} receptors. Considerable evidence indicates that these two receptors exert opposing effects on the expression of some behaviors, ranging from simple motor responses, such as wet dog shakes (WDS) and locomotor activity,[37,51−54] to more complex response patterns such as motor impulsivity.[55−58] A simple demonstration of the importance of this interaction was found in experiments investigating the effects of combinations of dexfenfluramine and the selective 5-HT_{2C} antagonist SB-242084.[39,59,60] In the absence of SB-242084,[60] dexfenfluramine produced 5-HT_{2C} receptor-dependent penile grooming in male rats with a mild incidence of 5-HT_{2A}-mediated behaviors, such as WDS and paraspinal muscle contractions (PMC[61,62]). Cotreatment with SB-242084 intensified 5-HT_{2A} (and 5-HT_{1B}) receptor-mediated behaviors, including WDS, PMC, hyperthermia, and hyperlocomotion (Figure 1B,D);[39] these effects were attenuated or blocked by the 5-HT_{2A} antagonist M100907.[39,59] These observations show that removal of 5-HT_{2C} receptor signaling unmasks a significant 5-$HT_{2A/1B}$ agonist action of dexfenfluramine.[39] In contrast, fluoxetine and citalopram did not elicit any of these behaviors to a significant degree either with or without SB-242084 treatment (Figure 1B,D) (see also refs 63 and 64). A similar unmasking of non-5-HT_{2C} receptor activity has been found in studies investigating the effects of the mixed 5-HT agonist/releaser mCPP in 5-HT_{2C} receptor KO mice.[65−67] In wild-type mice, mCPP reduced locomotor activity; however, 5-HT_{2C} KO mice showed a paradoxical increase in locomotion in response to

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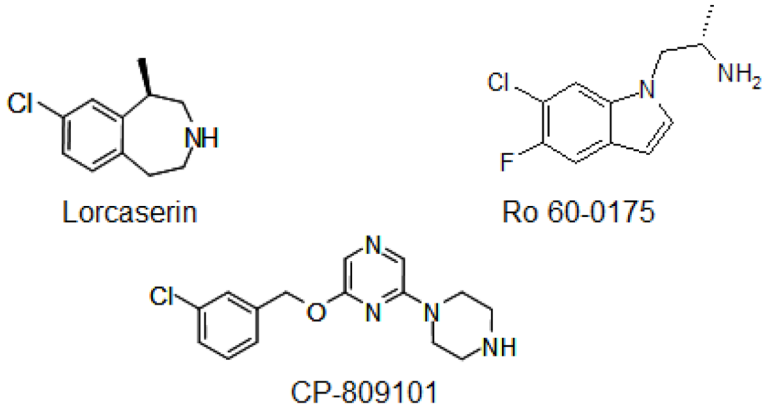
A. Selected 5-HT$_{2C}$ receptor agonists and 5-HT$_2$ receptor selectivity profile



	h5-HT$_{2C}$	h5-HT$_{2A}$	h5-HT$_{2B}$	Ratio 2C/2A	Ratio 2C/2B
Lorcaserin [1]	7.9 (1.0)	6.7 (1.0)	6.0 (1.0)	16	80
Ro 60-0175 [2]	7.5 (0.84)	6.4 (0.69)	9.1 (0.79)	13	0.03
CP-809101 [3]	10.0 (0.93)	6.8 (0.67)	7.2 (0.57)	1585	630

B. Lorcaserin, Ro 60-0175 and CP-809101 each reduce responding maintained by nicotine and food reinforcement

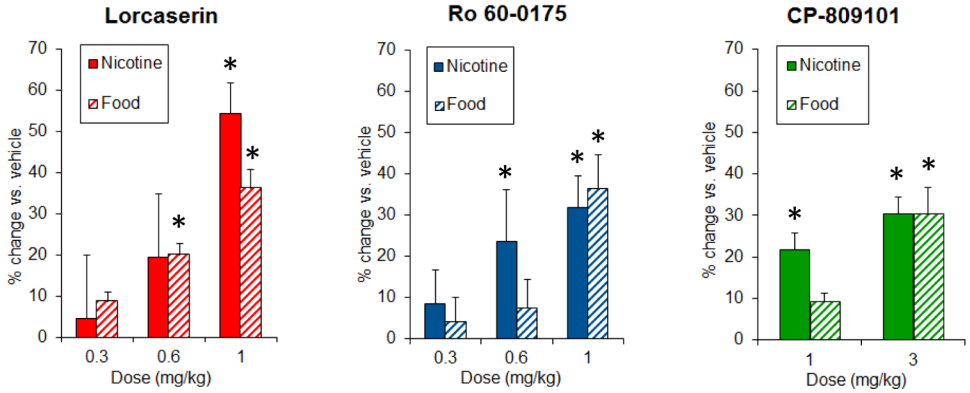


Figure 2. (A) Chemical structures of three 5-HT$_{2C}$ receptor agonists: the benzazepine derivative lorcaserin, the indolamine Ro 60-0175, and the piperazine derivative CP-809101. The table below summarizes agonist potency (pEC$_{50}$) and efficacy relative to a supramaximal concentration of 5-HT at respective 5-HT$_2$ receptor subtypes. Also, the selectivity ratio for 5-HT$_{2C}$/5-HT$_{2A}$ and 5-HT$_{2C}$/5-HT$_{2B}$ based on pEC$_{50}$ is presented. Reproduced with permission from ref 135. Copyright 2013 Springer International Publishing. (Original data used in ref 135 were from (1) Thomsen et al.,[86] (2) Porter et al.,[50] and (3) Siuciak et al.[113]) Because of differences between cell lines, receptor density, and functional readout, these data are best used for within-drug comparisons across 5-HT$_2$ receptor subtypes rather than between-drug comparisons. (B) The lower figure summarizes findings from three separate reports utilizing identical methods to measure effects of each 5-HT$_{2C}$ receptor agonist on either food (45 mg pellet) or intravenous nicotine (0.03 mg/kg/infusion), each available under a fixed ratio 5 with a 20 s time out (FR5TO20s) schedule of reinforcement (60 min session duration). Data is expressed as percentage decrease in the number of reinforcers earned compared to vehicle control. ■ = nicotine; □ = food. Note that for each drug there is no clear separation between doses that reduce responding for either nicotine or food. * $P < 0.05$ vs vehicle control. Data reprinted with permission from refs 87, 131, and 135. Copyright 2012 Nature Publishing Group, copyright 2012 Elsevier, and copyright 2013 Springer International Publishing, respectively.

mCPP. This was shown to result from an unmasking of 5-HT$_{1B}$ receptor activating effects of mCPP.[65,66] Taken together, these data highlight a difference in the degree of indirect 5-HT$_{2C}$ receptor agonism between the SSRI and releaser drug class. This difference may explain why obesity was treated more effectively compared to substance abuse. Indeed, Baumann and Rothman[36,68] proposed that 5-HT releasers and mixed 5-HT/DA releasers are viable approaches to treat psychostimulant and alcohol addictions.

Despite the fact that (dex)fenfluramine was used successfully to reduce appetite and treat obesity, it was found to induce cardiac valvulopathy and pulmonary hypertension in some individuals.[69−71] This resulted in the withdrawal of (dex)-fenfluramine from the clinic.[72] Despite their extensive usage and their ability to elevate extracellular 5-HT, SSRIs have not been associated with these complications.[73,74] In turn, this is a further example of a functional difference between elevated serotonin function produced by (dex)fenfluramine versus SSRIs, and it is reasonable to suspect that this could reflect the more subtle effects of SSRIs on extracellular 5-HT levels and concomitant 5-HT receptor interactions

On the basis of lessons learned from basic research and clinical findings with (dex)fenfluramine, evidence suggested that an ideal serotonergic-based antiobesity drug should activate

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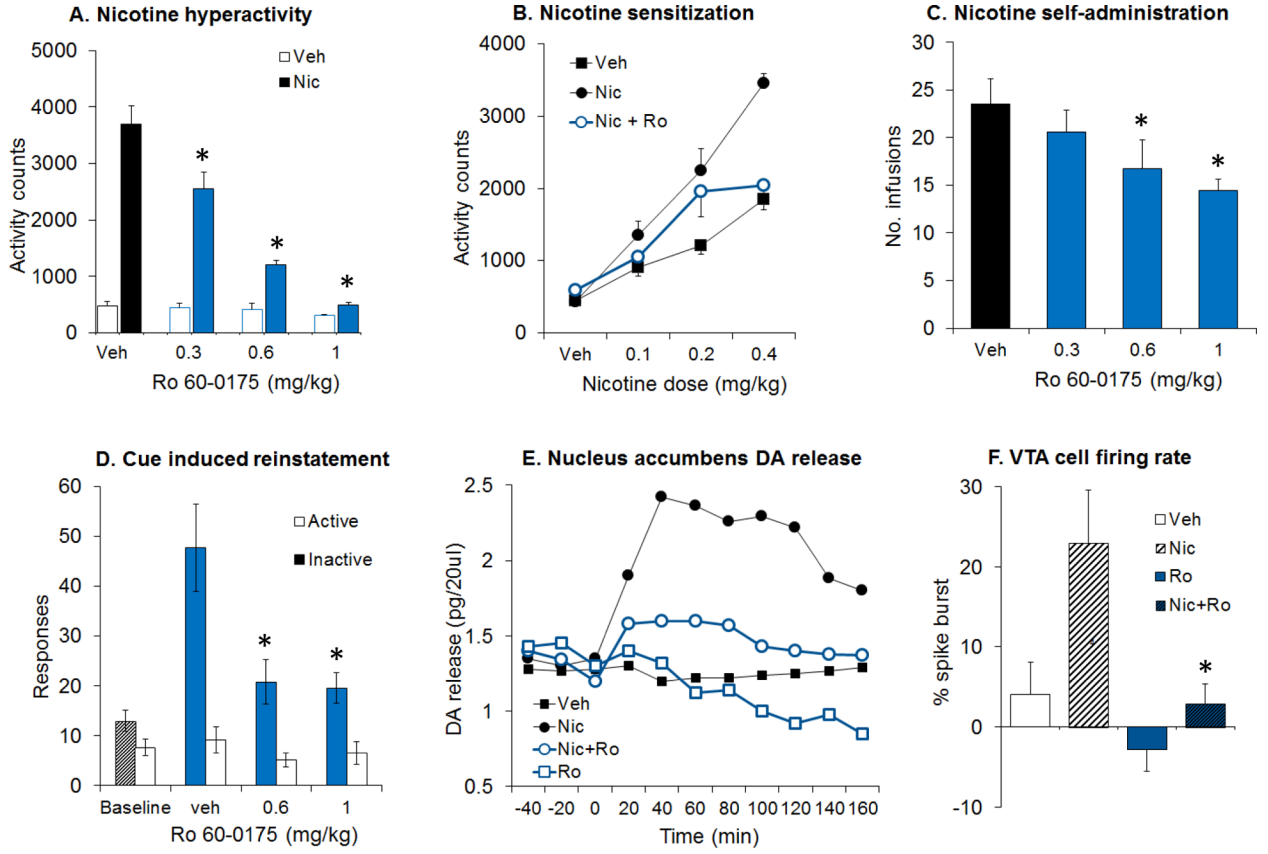

Figure 3. Summary of preclinical evidence to support potential for 5-HT_{2C} receptor agonists as treatments for smoking cessation using prototypic 5-HT_{2C} receptor agonist Ro 60-0175. (A) Ro 60-0175 (0.3−1 mg/kg SC) reduces the hyperactivity produced by acute nicotine (0.4 mg/kg SC) challenge in nicotine-sensitized rats. *$p < 0.05$ vs vehicle/nicotine pretreatment. (B) Ro 60-0175 (1 mg/kg SC) blocks the sensitization to the motor stimulant effects of nicotine. (C) Ro 60-0175 (0.3−1 mg/kg SC) reduces the self-administration of intravenous nicotine (0.03 mg/kg/infusion) in male, Long Evans rats. (D) Ro 60-0175 (0.6−1 mg/kg SC) reduces the reinstatement of nicotine-seeking behavior produced by presentation of cues. (E) Ro 60-0175 (1 mg/kg IP) reduces nicotine-induced elevation in mesoaccumbens DA release measured by microdialysis. Male Sprague−Dawley rats were treated for 10 days with nicotine (1 mg/kg IP) prior to the microdialysis experiment. (F) Ro 60-0175 (0.1 mg/kg IV) reduces the nicotine-induced elevated firing pattern of VTA DA neurones. Data represent the mean ± SEM difference between the percentage of spikes occurring in bursts during baseline period compared to that post drug treatment. Data in (A) and (B) were adapted with permission from ref 120. Copyright 2001 Springer International Publishing. Data in (C) and (D) were adapted with permission from ref 131. Copyright 2012 Elsevier. Data in (E) were adapted with permission from ref 126. Copyright 2004 John Wiley & Sons. Data in (F) were adapted with permission from 125. Copyright 2004 American Society for Pharmacology and Experimental Therapeutics.

5-HT_{2C} receptors while being devoid of activity at 5-HT_{2B} receptors, which were subsequently identified as the target for cardiac valvulopathy and pulmonary hypertension.[75−77] This provided the impetus for the identification and development of selective 5-HT_{2C} receptor agonists as new antiobesity agents.[33,78−80] The characteristics of such drugs are reviewed in the following section.

5-HT_{2C} RECEPTORS REGULATE BEHAVIORS MOTIVATED BY BOTH DRUGS AND FOOD

Evidence for the importance of the 5-HT_{2C} receptor in feeding behavior was provided by the obese phenotype of the 5-HT_{2C} KO mouse,[81] and attenuation of the anorectic effects of dexfenfluramine both in these mice,[82] and by selective 5-HT_{2C} receptor antagonists in WT animals.[41,42] The test compound Ro 60-0175 was identified as the first apparently selective 5-HT_{2C} receptor agonist.[83] Ro 60-0175 reduced the consumption of a palatable diet in rats, providing direct evidence that an orthosteric 5-HT_{2C} receptor agonist has anorectic property.[83] This finding has since been replicated in acute feeding studies using multiple 5-HT_{2C} receptor agonists of varying selectivity,[33,78,84] including lorcaserin[67,85−87] (Figure 2A). Studies with lorcaserin have also been extended into obesity models such as the diet-induced obese (DIO) and Levin rat. In both models, lorcaserin reduced food consumption, body mass, and fat content following chronic (28 day) treatment.[86,88]

A role for 5-HT_{2C} receptors in the regulation of forebrain DA systems is well-established based on evidence from experiments using electrophysiological and biochemical techniques.[89−95] This 5-HT_{2C} receptor-mediated modulation of DA function suggested to us that 5-HT_{2C} receptor agonists should affect behaviors motivated by drugs of abuse as well as food. Initially, we focused on interactions between 5-HT_{2C} receptor agonists and the psychostimulant cocaine. Thus, Grottick et al.[96] reported that Ro 60-0175 reduced the stimulant and reinforcing effects of cocaine, measured using locomotor and self-administration assays, respectively. The doses that produced these effects overlapped with doses of Ro 60-0175 that also reduced food-maintained behaviors,[83,96,97] and these effects were blocked by the 5-HT_{2C} receptor antagonist SB-242084.[60] We also showed that Ro 60-0175 reduced reinstatement of cocaine-seeking in animals with a previous history of cocaine

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Table 1. Comparison of Lorcaserin Doses Necessary To Affect Various Behaviours Related to Food Motivation or Nicotine Dependence[a]

Behaviour	0.1mg/kg	0.3mg/kg	0.6mg/kg	1mg/kg
Reduction of palatability-induced feeding [ref. 87]	-	↔	-	+
Reduction of food intake under a progressive ratio schedule [ref. 87]	-	↔	+	+
Reduction of nicotine-induced hyperactivity [ref. 87]	↔	+	+	+
Reduction of nicotine self-administration [ref. 87, 136]	-	↔	(+)	+
Reduction of reinstatement of nicotine self-administration [ref. 87]	-	+	+	+
Reduction of nicotine impulsivity (5-choice task) [ref. 87, present]	↔	+	+	+
Reduction of nicotine somatic withdrawal signs [present]	-	-	-	↔
Plasma levels of lorcaserin (C_{max}; ng/ml) [ref. 135]		36 ng/ml		120 ng/ml

[a]Note the relative sensitivity of premature responding and reinstatement of nicotine seeking behavior to lorcaserin pretreatment. Also shown is lorcaserin plasma exposure at equivalent doses. Data sources are indicated in superscript. For comparison, the clinical lorcaserin exposure at the 10 mg bid regimen is reported as 44 ng/mL steady state, 57 ng/mL C_{max} (based on FDA document NDA 22-529). Key: [−] not tested (at specific dose), [↔] no effect, [(+)] nonsignificant trend, [+] significant effect.

self-administration.[96,98] Subsequent research by multiple groups has confirmed and extended these findings.[99−112] Of particular note, Howell and co-workers[110] showed that Ro 60-0175 reduced cocaine self-administration and reinstatement of cocaine seeking in cynomolgus monkey, thus extending these findings to a primate species. Recently, Wöhr et al.[112] described an inhibitory effect of the highly selective 5-HT_{2C} receptor agonist, CP-809101,[113] on amphetamine-induced appetitive ultrasonic vocalisations. This is of interest because it demonstrates a modulatory effect of a 5-HT_{2C} receptor agonist on a nonmotor expression of drug reward. Overall, these findings provide a strong case that 5-HT_{2C} receptor agonists inhibit both drug-taking and drug-seeking behaviors for psychomotor stimulants (see Howell and Cunningham[114] for a recent review).

One of the most widespread and prevalent addictions is to tobacco, with nicotine being generally accepted as the psychoactive substance responsible for this dependence and addiction.[115] Tobacco use is associated with multiple adverse effects on health, and there are few effective treatments for this behavior.[116−119] Consequently, we have investigated interactions between 5-HT_{2C} receptor agonists and nicotine. In 2001, it was reported that Ro 60-0175 reduced nicotine self-administration and the locomotor stimulant effect of nicotine in rodents.[120] Sensitization to the stimulant effects of chronically administered nicotine (likely mediated by $\alpha_4ß_2$ receptors within the VTA; see refs 121−124) was also prevented by concomitant Ro 60-0175 treatment.[120] Parallel investigations by Esposito and co-workers demonstrated that equivalent regimens of Ro 60-0175 treatment reduced the elevated accumbens DA release and VTA cell firing elicited by chronic treatment with nicotine.[125,126] These effects implicate a modulatory effect of 5-HT_{2C} receptors on nicotinic $\alpha_4ß_2$ receptor signaling within the VTA, which is regarded as a critical locus for mediating the reinforcing effects of nicotine[127−130] (summarized in Figure 3). Subsequently, we have shown that Ro 60-0175 also reduced the reinstatement of nicotine-seeking behavior elicited by a priming injection of nicotine and by nicotine-associated cues.[131] Smokers are particularly vulnerable to relapse even after a year of abstinence;[132] therefore, the ability of 5-HT_{2C} receptor agonists to prevent reinstatement of nicotine seeking suggests that these drugs may be effective in preventing relapse to nicotine seeking. Quarta et al.[133] also demonstrated that Ro 60-0175 attenuated the cueing effects of nicotine in a drug discrimination assay, suggesting that 5-HT_{2C} receptor stimulation alters the subjective effects of nicotine (see also Zaniewska et al.[134]).

More recently, we[87,135] and Levin and co-workers[136] have shown that lorcaserin produces similar effects to those of Ro 60-0175 on measures of nicotine-induced hyperactivity, self-administration, discrimination, and reinstatement of nicotine-seeking behavior. Nicotine increases responding for a conditioned reinforcer,[137] an effect consistent with the notion that nicotine is addictive in part because of its reinforcer-enhancing effects.[138] We have found that lorcaserin blocks the effect of nicotine to enhance responding for a conditioned reinforcer.[137] Most recently, we reported that lorcaserin prevents the ability of nicotine to enhance the efficacy of brain stimulation reward.[139] Collectively, these findings show that lorcaserin (and 5-HT_{2C} agonists in general) diminishes a range of behaviors that likely contribute to the maintenance of nicotine-seeking behavior and the state of nicotine dependence (Table 1). As with Ro 60-0175, the doses of lorcaserin that produce these effects are very similar to those that alter feeding-related behaviors. Plasma levels of lorcaserin over the effective dose range (i.e., 0.3−1 mg/kg) are also similar to those reported in participants in clinical trials of lorcaserin for weight loss (44 ng/mL steady state; 57 ng/mL C_{max};[135] Table 1). Taken together, these data from rats and humans indicate that investigations of lorcaserin in smoking cessation trials would require a similar dose regimen and exposure to that used successfully in obesity trials.[140−144]

One consequence of chronic nicotine use that contributes to its abuse liability is physical dependence. This aspect of nicotine dependence may not be reliably affected by 5-HT_{2C} receptor agonist treatment. Rats can be made physically dependent through chronic delivery of nicotine via an osmotic minipump primed to produce blood levels of nicotine equivalent to those

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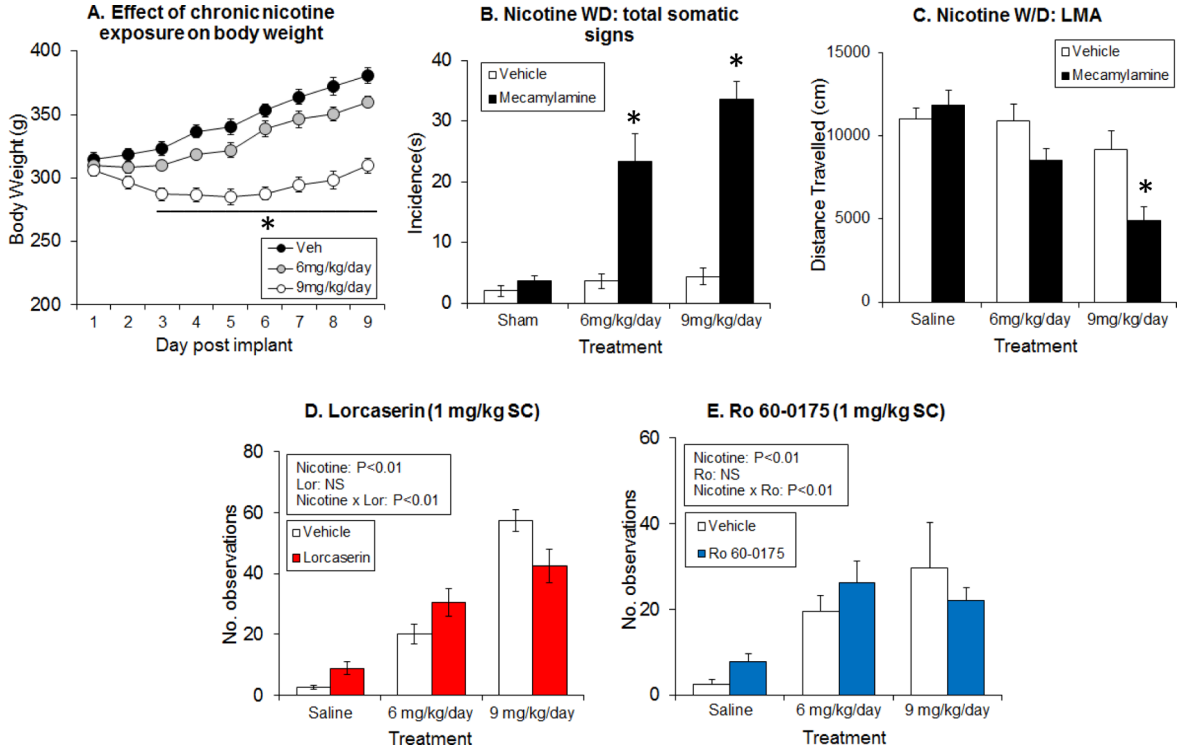

Figure 4. Characterization of Ro 60-0175 and lorcaserin against somatic signs of nicotine-precipitated withdrawal. Male Wistar rats were either implanted SC with osmotic minipump primed to deliver saline (sham) or nicotine at 6 or 9 mg/kg/day. (A) Body weight measured over 9 days post pellet implantation. Some change in weight gain was noted, particularly in the 9 mg/kg/day group. On day 9, withdrawal was precipitated by an acute injection of mecamylamine (1 mg/kg SC) or vehicle control. (B) Somatic withdrawal signs (e.g., chewing, ptosis, wet dog shakes, twitches) and (C) locomotor activity were measured over the subsequent 30 min period. Both somatic signs and hypolocomotion was evident in rats treated with the nicotine + mecamylamine combination. * $P < 0.05$ vs respective vehicle treated group. In separate groups of rats prepared with minipumps primed to deliver saline or nicotine at 6 or 9 mg/kg/day, the effect of acute pretreatment with either (D) lorcaserin (1 mg/kg SC; 30 min pretreatment) or (E) Ro 60-0175 (1 mg/kg SC; 30 min pretreatment) was investigated against mecamylamine (1 mg/kg) precipitated withdrawal in Wistar rats. Testing was conducted 9 days post minipump implantation. Neither treatment significantly affected overall incidence of withdrawal signs in each nicotine group.

of heavy smokers (i.e., 20−40 ng/mL; see refs 145 and 146). Withdrawal can be precipitated by removing the pump or by an acute mecamylamine injection, with a resultant expression of somatic signs such as writhing, teeth chatter, ptosis, and hypolocomotion[145,146] (Figure 4A−C). In rats implanted with minipumps delivering nicotine (6 or 9 mg/kg/day for 8 days), treatment with Ro 60-0175 or lorcaserin immediately before mecamylamine injection failed to relieve any of these somatic signs (Figure 4D,E). This lack of effect may not be too surprising since a dysregulation of cholinergic systems both centrally and peripherally likely contributes to the state of physical dependence to nicotine[145,146] and 5-HT_{2C} receptors are almost exclusively localized to the CNS.[147] A single report has described a positive effect of Ro 60-0175 against an affective component of nicotine withdrawal measured as immobility in a forced swim test.[148] This suggests that perhaps certain central signs of nicotine withdrawal can be relieved by 5-HT_{2C} receptor agonists. Clinically, it is likely that affective aspects of nicotine abstinence, such as anhedonia, contribute to relapse more than somatic aspects,[149−151] so further work is necessary to build on this interesting observation.

OBESITY AND SUBSTANCE ABUSE POST 1987: OVERLAPPING RESEARCH QUESTIONS

Since the inaugural Serotonin Club meeting, research into the biological and behavioral bases of obesity and substance abuse has converged and the scope of addictions research has broadened.[1] It is now generally accepted that, in a significant subpopulation of obese individuals, behaviors common to substance abuse contribute to the clinical phenotype.[152−156] The recognition that behavioral and neurobiological commonalities occur between obesity and drug addiction has resulted in debate as to whether both overeating in obesity and excessive drug use in addiction should be considered as a common brain disorder and whether this should be included as a diagnostic category in DSM-V[157] (Table 2).

Investigations into the neurobiology of impulsive and compulsive action has become a central theme of addiction research. Impulsivity is not a unitary construct and may be subcategorized into impulsive action and impulsive choice.[158−160] Impulsive action (behavioral disinhibition) is characterized by acting prematurely or failing to inhibit responding. Specific measures of impulsive action include premature responding on the 5-choice serial reaction time task (5-CSRTT), responding on go-no go and stop-signal tasks, as well as responding maintained on a differential reinforcement of low (DRL) rate of responding schedule.[161] Impulsive choice can be assessed using a delay-discounting task in which the preference for a small immediate reward over a larger, but delayed, reward is measured. Compulsivity reflects inappropriate habitual actions, with no relation to outcomes and typically with undesirable consequences.[162]

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Table 2. Aberrant Brain Functions and Behaviours Contributing to Addiction and Obesity and the Brain Regions Implicated in Such Dysfunction[a]

disrupted function	implicated brain region	influence of 5-HT_{2C} receptor agonists?
Impaired inhibitory control (to drug intake in addiction and food intake in obesity)	Prefrontal cortex, anterior cingulate gyrus	5-HT_{2C} agonists ↓ measures of relapse and impulsive action [e.g., refs 57, 87, 98, 103−107, and 192]
Enhanced reward (to drugs in addiction to food in obesity)	Nucleus accumbens, ventral pallidum, hypothalamus	5-HT_{2C} agonists ↓ responding for, and intake of, drugs and food [e.g., refs 84, 87, 96, 97, 107, 110, 131, and 136]
Conditioning/habits (to drugs and drug cues in addiction, to food and food cues in obesity)	Amygdala, hippocampus, dorsal striatum	5-HT_{2C} agonists ↓ responding for secondary cues paired with drugs or food [e.g., ref 137] and ↓ compulsive behaviors [e.g., refs 83, 186, and 191]
Enhanced motivation/drive (to consume drugs in addiction, to consume food in obesity).	Orbitofrontal cortex, mesenecephalic DA nuclei (VTA, SNR)	5-HT_{2C} agonists ↓ responding for, and intake of, drugs and food [e.g., refs 84, 87, 96, 97, 107, 110, 131, and 136]

[a]The majority of these identified brain regions contain 5-HT_{2C} receptors as based on expression studies conducted in rodent, primate, and human brain tissue [e.g., see refs 246−248.]. Various 5-HT_{2C} receptor agonists, including lorcaserin, have been shown to modify these aberrant behaviours in a manner suggestive of positive benefit (see text and references). Table adapted from ref 157. Copyright 2007 American Psychiatric Association.

Soubrie[163] recognized that a consequence of lesioning central 5-HT systems using agents such as 5,7-DHT resulted in impulsive-type behavior, typically seen as increased responding under conditions of punishment or in situations requiring a response delay for reinforcement. Central 5,7-DHT lesions reliably increased premature responses in the 5-CSRTT[164−166] and increased responding on a DRL schedule of reinforcement, resulting in shorter inter-response time intervals (IRTs) and lowered response efficiency.[167−169] These effects of forebrain 5-HT depletion are reproduced by selective 5-HT_{2C} receptor antagonists. For example, SB-242084 reliably increases premature responding in the 5-CSRTT and produces a leftward shift in the distribution of IRTs on a DRL schedule[55−57,170] (Figure 5A,B). Thus, behaviors characterized as impulsive action produced by central 5-HT lesions are mimicked by acute pharmacological blockade of the 5-HT_{2C} receptor, suggesting that the lesion-induced changes reflect a reduction in signaling through the 5-HT_{2C} receptor. In contrast, mixed findings have been reported for the effects of 5,7-DHT lesions of 5-HT neurones on impulsive choice. Thus, one study found no effect of 5-HT depletion on delay discounting,[166] whereas others found that the behavior of 5-HT-depleted rats was consistent with a shift toward impulsive choice.[171,172] Further studies are needed to determine whether serotonergic mechanisms differentially affect impulsive action and choice.[166,173,174]

The possible relationship between impulsivity and addiction has become a significant focus at both the preclinical and clinical levels. Broadly speaking, it seems that impulsivity may influence multiple aspects of addictive behavior.[162,175] First, impulsiveness may be a predisposing factor that initially promotes the acquisition of addictive behaviors. For example, those rats characterized as high impulsive (HI) may be more prone to acquire self-administration of cocaine,[176−178] nicotine,[179] and palatable food[180] compared to that of low impulsive individuals (LI). Second, the transition from "casual" drug/food consumption to a state of compulsive seeking and dependence[181−184] may also be influenced by trait impulsivity. For example, in one study, a subpopulation of rats initially characterized as HI were subsequently trained on a schedule of cocaine availability and concomitant punishment. These HI rats were more likely to transition from controlled to compulsive drug-seeking behavior relative to their LI counterparts.[185] This transition may also be exacerbated by central 5-HT lesions as well as acute 5-HT_{2C} receptor blockade with SB-242084.[186] Third, relapse to drug-seeking behavior following a period of abstinence is more likely in rats characterized as HI prior to acquiring cocaine self-administration.[177,187,188] An emerging line of research from Cunningham, Moeller, and co-workers[189,190] suggests that HI rats with high responsivity to cocaine-paired cues may express biomarkers consistent with reduced 5-HT_{2C} receptor tone within the prefrontal cortex relative to their LI counterparts.

Given these associations between impulsive traits and addictive behavior, serotonin acting via 5-HT_{2C} receptors could potentially influence addiction indirectly via its effects on impulsive behavior. From a treatment perspective, 5-HT_{2C} receptor agonists may be helpful by inhibiting impulsivity in at least two ways. First, in relation to the transition from casual to compulsive drug use, and second, to relapse.

Relatively few studies have examined the effects of 5-HT_{2C} receptor ligands on compulsive behaviors. Martin et al.[83,191] reported that Ro 60-0175 reduced compulsive behaviors,

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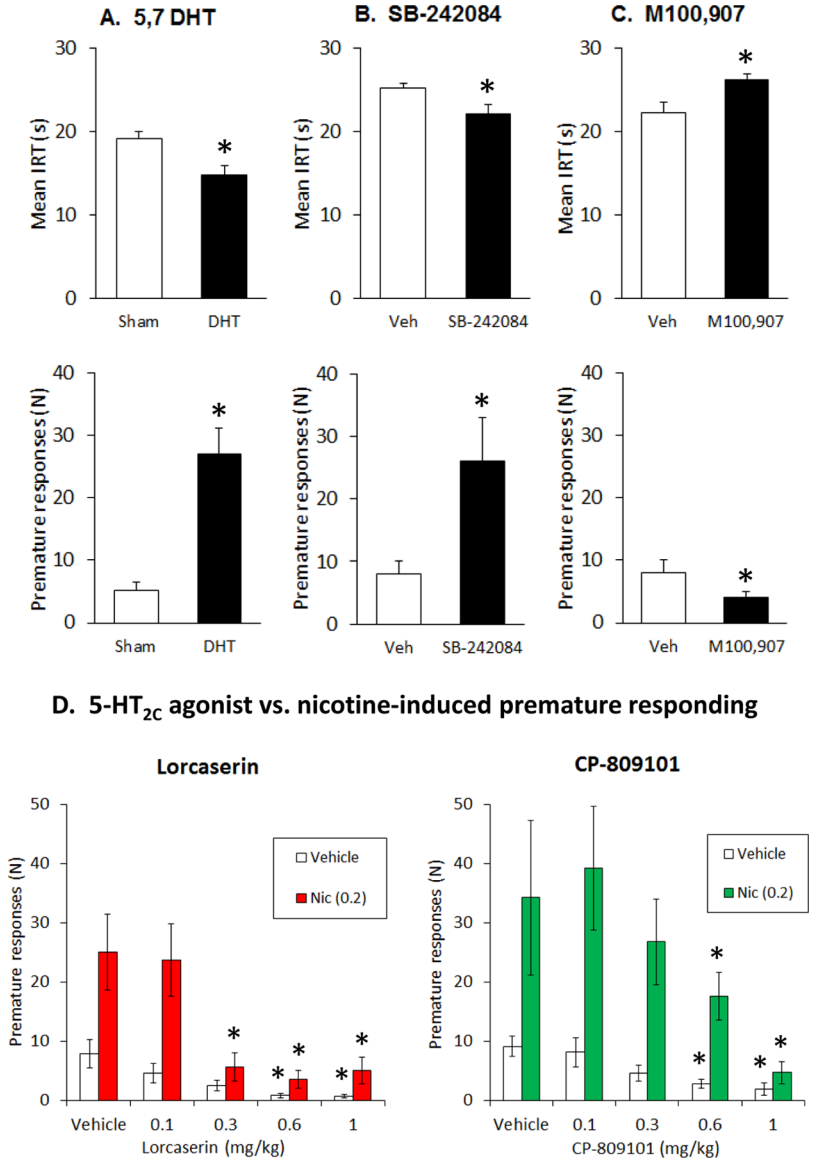

Figure 5. Pharmacological manipulation of 5-HT$_2$ receptor activity affect measures of motor impulsivity. (A–C) Comparison among 5,7-DHT lesions, the 5-HT$_{2C}$ antagonist SB-242084, and the 5-HT$_{2A}$ antagonist M100907 on two measures of impulsive action. Impulsive action was measured as mean inter-response time (IRT) in a DRL20 task and premature responding in the serial 5-choice task. Comparison between 5,7-DHT lesions and SB-242084 increase measures of impulsive action, i.e., reduce IRT in a DRL20 task and elevate premature responding in the 5-CSRTT. In contrast the 5-HT$_{2A}$ antagonist M100907 produces the opposite profile, i.e., increase IRT in a DRL20 task and decrease premature responding in 5-CSRTT. (D) Effect of the 5-HT$_{2C}$ receptor agonists lorcaserin (0.1–1 mg/kg SC) and CP-809101 (0.1–1 mg/kg SC) on premature responding in the 5-CSRTT (0.6s SD, 5s ITI, 100 trials) in rats pretreated with either vehicle or nicotine (0.2 mg/kg SC). Consistent with previous reports [see refs 87, 133, and 245], nicotine promotes premature responding, an effect blocked by both lorcaserin and CP-809101. Both 5-HT$_{2C}$ receptor agonists also reduced premature responding in vehicle-pretreated rats with minimal effect on other performance measures such as omissions, response speed, and accuracy at threshold doses (lorcaserin = 0.3 mg/kg SC; CP-809101 = 0.6 mg/kg SC). *$P < 0.05$ vs relevant control group. Data in (A–C) were adapted from refs 55, 165, and 169. Copyright 2003 Springer International Publishing, copyright 2000 Springer International Publishing, and copyright 1995 Elsevier, respectively. See text and the original references for further details.

measured in a schedule-induced polydipsia model in the rat and as 8-OH DPAT-induced scratching in the squirrel monkey. More recently, the nonselective 5-HT$_{2C}$ receptor agonist mCPP was shown to reduce the escalation of cocaine-seeking behavior[186] in a model of compulsive drug use. This suggests a potential for 5-HT$_{2C}$ receptor activation to modify the transition from recreational to compulsive drug use and could be a promising avenue for future work.

Relapse to drug seeking is most marked in animals with high levels of impulsive action, and 5-HT$_{2C}$ receptor agonists are particularly effective in dampening impulsive action, measured as premature responses in the 5-CSRTT[57,133,192] (Figure 5D). Several studies have now examined the effects of 5-HT$_{2C}$ receptor agonists in reinstatement procedures. Relapse to both drug- and food-seeking behavior may be triggered by a variety of stimuli, including cues previously paired with drug taking as well as a priming injection of the drug.[193−195] We previously reported that Ro 60-0175 inhibited reinstatement of nicotine-seeking behavior elicited by both cues and nicotine.[131] Lorcaserin reduced reinstatement elicited by a combination of conditioned cues and a priming injection of nicotine,[87] which may model the multifactorial nature of relapse triggers

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experienced by smokers.[196] Similar preclinical findings have been reported for systemically administered 5-HT_{2C} receptor agonists on cocaine reinstatement.[96,98,103,104,107] Microinjections of the 5-HT_{2C} receptor agonist MK212 into the prefrontal cortex, a brain region implicated in the regulation of impulsive behavior,[162,197,198] also reduced the reinstatement of cocaine seeking.[106] Collectively, these data suggest that 5-HT_{2C} receptor agonists improve aspects of inhibitory control, with potential benefit for preventing relapse following a period of abstinence.

CLINICAL EXPERIENCE WITH 5-HT_{2C} RECEPTOR AGONISTS: LORCASERIN

Despite significant interest from several pharmaceutical companies in developing selective 5-HT_{2C} receptor agonists, there are published reports for only two compounds of this class in the clinic at Phase II and beyond. Lorcaserin, identified and developed by Arena Pharmaceuticals, is the most advanced 5-HT_{2C} receptor agonist. It was approved in combination with lifestyle management for the treatment of obesity by the FDA in June 2012.[199] Approval was largely based on three Phase III trials, two of which, BLOOM and BLOSSOM, were conducted in adults categorized as obese with at least one comorbid condition.[142,143] A third Phase III study in overweight/obese patients with poorly controlled type 2 diabetes (BLOOM-DM) was also conducted.[144] Each study was of 1 to 2 years in duration. A meta-analysis of the BLOOM and BLOSSOM trials has been recently published.[200] This meta-analysis is the largest obesity pharmacotherapy data set published to date in the U.S. and includes data from 6388 patients, approximately half of whom received lorcaserin at 10 mg bid. By week 52, approximately twice as many lorcaserin-treated patients relative to placebo-treated controls achieved a weight loss of ≥5% (47.1 vs 22.6%; lor vs placebo) or ≥10% (22.4 vs 8.7%; lor vs placebo). This meta-analysis also provides information concerning the safety and tolerability of the 10 mg bid lorcaserin regimen. The most common adverse effects were headache, dizziness, and nausea. The incidence of FDA-defined valvulopathy, which was a significant adverse effect associated with use of (dex)fenfluramine, was considered to be negligible.[201] Some psychoactive effects ("detached", "spaced-out", "floating") were reported in drug-experienced subjects at supratherapeutic doses,[202] and this likely contributed to lorcaserin being designated a Schedule IV class drug by the DEA.[203]

In early 2014, Arena/Eisai initiated a randomized, double-blind, placebo-controlled Phase II trial to assess the efficacy of lorcaserin as an aid for smoking cessation.[204] Over 600 active smokers (defined as dependent on nicotine and smoking on average 18 cigarettes per day) were assigned to one of three treatment groups, comprising placebo or lorcaserin 10 mg once or twice daily. Treatments were administered for 12 weeks, with the primary end point of continuous quit rate during weeks 9–12. This end point was met by 5.6% subjects in the placebo group, 8.7% in the lorcaserin once daily group, and 15.3% in the lorcaserin 10 mg bid group. Thus, treatment with lorcaserin at the FDA approved dose schedule for obesity resulted in a significant improvement in continuous quit rate compared to that with placebo.[205] Side effects were similar to those reported in the obesity trials, and a reduction in bodyweight was observed, suggesting further benefit to this treatment. Although at the time of writing no further trials have been publicly disclosed, it is hoped that future clinical investigations will continue from these highly promising observations.

The second drug, vabicaserin,[206] was identified and developed by Wyeth Pharmaceuticals (now Pfizer) and trialed in 289 hospitalized patients with acute schizophrenia. The idea that vabicaserin might have antipsychotic activity was based on the modulatory effects of 5-HT_{2C} receptor agonists on forebrain DA and their profile of behavioral effects in animal models predictive of antipsychotic efficacy.[95,207] Vabicaserin induced a significant improvement on the primary end point of PANNS positive symptom scale relative to placebo in the lower (200 mg/day), but not higher (400 mg/day), dose group.[208] Effect size at the 200 mg/day dose was almost equivalent to the olanzapine positive control, with no weight gain, an acceptable tolerability, and no safety alerts. Subsequent *in silico* modeling predicted PANNS improvements in a virtual trial design, although the effect size was determined to be of limited clinical benefit relative to existing neuroleptics.[209] At this time, there is no publicly disclosed information relating to its present status or possible effect in indications of obesity and addiction.

FUTURE DIRECTIONS

There are several exciting opportunities for exploring the potential of 5-HT_{2C} receptor agonists as treatments for addictive disorders. Now that lorcaserin has been approved for the treatment of obesity, this presents a number of different opportunities for examining its effects and mode of action related to feeding, addiction, and associated behaviors in humans. Food consumption is a necessity for energy intake and growth, and as such, eating behavior is regulated by multiple biological systems linked to hunger, reward, and hedonic mechanisms.[153,155,210−212] As a result, there are likely many paths to gaining weight, and lorcaserin only reached a primary end point of placebo-corrected weight loss of >5% in a subpopulation of patients (47.1 vs 22.6% in placebo group[200]). However, the scale of the BLOOM and BLOSSOM trials combined may be sufficient to identify differences between those individuals that responded favorably to lorcaserin compared to those that did not. This could shed light on the underlying neurobiological and behavioral mechanisms responsible for the antiobesity effects of lorcaserin.

Given that 5-HT_{2C} receptor agonists, including lorcaserin, modulate impulsive behaviors central to addiction, an evaluation of this drug in associated overeating disorders, such as binge eating disorder,[213,214] would be of particular interest. Preclinical studies demonstrate that 5-HT_{2C} receptor agonists reduce feeding motivated by hunger and palatability,[83−88,97,135,215] consistent with these drugs influencing both homeostatic and hedonic drivers of feeding behavior. Animal models of binge eating disorder have been described,[216−218] some with overlap to limited access palatability tests. As yet, the effect of 5-HT_{2C} receptor agonists in binge eating models has not been reported, but such experiments may provide impetus to the study of lorcaserin against this clinical condition.

Examining the effects of lorcaserin on measures of drug addiction is an obvious area for development. Preclinical work indicates that there is a potential for lorcaserin to treat nicotine dependence and psychostimulant and alcohol abuse.[114,219−223] The potential therapeutic benefit for lorcaserin as a treatment to support smoking cessation is already being explored with positive initial results.[205] Treatments that reduce impulsivity may offer promising approaches aimed at preventing relapse and increasing drug abstinence.[162,175] Atomoxetine is a

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nonstimulant drug approved for ADHD that reduces measures of impulsivity in animals.[170,224−226] Atomoxetine also reduces reinstatement of cocaine-seeking and has been proposed as a potential therapy for preventing relapse and promoting abstinence.[178,227,228] A similar argument can be made for lorcaserin. Indeed, there are multiple points at which 5-HT_{2C} receptor agonists may serve to stabilize aberrant processes contributing to the clinical phenotype of addiction and obesity (Table 2).

A further opportunity relates to the development of newer 5-HT_{2C} receptor agonists. While lorcaserin is the first clinically approved 5-HT_{2C} receptor agonist, there is scope to develop drugs with greater agonist selectivity for the 5-HT_{2C} receptor particularly relative to the 5-HT_{2A} and 5-HT_{2B} subtypes. Indeed, there has been debate about the actual selectivity of lorcaserin.[229] CP-809101 has been reported to have a 5-HT_{2C} vs 5-$HT_{2A/2B}$ receptor selectivity of 600−1500-fold, compared to 15−80-fold for lorcaserin, albeit based on *in vitro* screening using heterologous cell systems;[86,113] see Figure 2A. The occupancy level of central 5-HT_{2C} receptors by lorcaserin at the clinically approved 10 mg bid dose is unknown because of the absence of a suitable biomarker (however, see Granda et al.[230] regarding development of a potential 5-HT_{2C} receptor selective PET ligand). Given concerns about deleterious effects of off-target 5-HT_{2B} and 5-HT_{2A} receptor agonism, the need for caution during clinical development is significant. Availability of a 5-HT_{2C} receptor agonist with greater selectivity and, second, of imaging biomarkers to define target (and off-target) occupancy could significantly improve therapeutic response by enabling a more optimal dosing regimen.

In addition to direct orthosteric agonists at the 5-HT_{2C} receptor, the identification of positive allosteric modulators (PAMs) at this receptor may conceivably lead to improved therapeutics. First, PAMs would amplify endogenous signaling through the 5-HT_{2C} receptor, likely resulting in a more physiologically relevant enhancement of function compared to a direct orthosteric agonist. Second, because of a generally higher sequence divergence in allosteric sites relative to the conserved orthosteric domain, PAMs could potentially achieve higher receptor selectivity than orthosteric agonists.[231,232] Indeed, some 5-HT_{2C} receptor PAMs have been reported,[233,234] although as yet the pharmacological profiles of these compounds have not been widely reported. Another area for 5-HT_{2C} receptor agonist development might emerge from compounds having functional selectivity (biased agonism) for specific intracellular signaling pathways.[235] 5-HT_{2C} receptors couple to multiple intracellular pathways including PLC and PLA_2,[235,236] and pharmacological evidence using recombinant cell-based systems suggests that nonselective 5-HT_2 agonists such as mCPP and quipazine may differentially activate these signaling pathways downstream from the 5-HT_{2C} receptor.[237] Currently, it is unknown whether this example of functional selectivity could be translated into any therapeutic gain, although this does open up an interesting opportunity for future drug discovery.[235,238−240] A further approach is the identification of compounds with 5-HT_{2C} receptor agonist activity combined with antagonist activity at the 5-HT_{2A} receptor. Experimental evidence supports a potential synergy between these two activities, raising the theoretical possibility that a single drug possessing both pharmacological properties may be a superior therapeutic compared to either alone.[58,241−244]

In concluding, lorcaserin is the first serotonin-based therapy to be approved by the FDA since the mixed 5-HT/NA reuptake inhibitor sibutramine. It will be interesting to observe the future investigation plan and outcomes for this drug and other 5-HT_{2C} receptor agonists in the clinic and to see whether this drug class can emerge as a new treatment approach for clinical conditions characterized as addictions, including certain eating disorders. This would also represent a test of the translational value to the various preclinical models that consistently suggest efficacy of 5-HT_{2C} receptor agonists in these conditions.

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