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Allosteric modulation of the 5-HT₃ receptor

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Abstract

5-Hydroxytryptamine type 3 (5-HT₃) receptors are ligand-gated ion channels that play important roles in depression, anxiety, substance abuse, emesis, inflammatory pain, spinal nociception, gastrointestinal function, and cardiovascular reflexes. Probably the most studied modulators of 5-HT₃ receptors are the high affinity competitive ‘setron’ antagonists typified by ondansetron. However, there exists a broad range of compounds that modulate the 5-HT₃ receptor, not through the orthosteric site but by binding to allosteric sites. Most notable are therapeutic compounds ascribed to certain targets but that allosterically modulate 5-HT₃ receptors at clinically relevant concentrations.

Keywords

anesthetics; alcohols; antidepressants; antipsychotics; cannabinoids

Introduction

The 5-HT₃ receptor is a member of the Cys-loop ligand-gated ion channel (LGIC) superfamily which includes the nicotinic acetylcholine, γ -aminobutyric acid type A (GABA_A), glycine and ZAC receptor ion channels [1]. Five genes encoding for individual subunits (5-HT_{3A-E}) have been identified within the human genome [2*]. However, current knowledge of 5-HT₃ receptor pharmacology is heavily biased towards information from human and rodent homomeric 5-HT_{3A} receptors expressed in recombinant cells or native 5-HT₃ receptors of unknown subunit composition expressed in rodent cells (rodents have genes only for 5-HT_{3A} and 5-HT_{3B} subunits).

Agonists and positive modulators of 5-HT₃ receptors are not favorable for clinical use because of enhanced anxiety and pro-emetic effects. In contrast, antagonists are successfully used to treat chemotherapy-induced vomiting, post-operative nausea and vomiting (PONV), alcohol craving and irritable bowel syndrome with diarrhea. Modulators of 5-HT₃ receptors have also been suggested to have therapeutic relevance for schizophrenia, anxiety, cognition and nociception [3].

Most members of the LGIC superfamily have several different subunits that can assemble to form multiple receptor subtypes. Each subunit structurally influences channel properties; hence heteromeric receptors provide diversity in pharmacological and biophysical properties within a receptor family. Allosteric modulators bind to a site distinct from the orthosteric

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site (the endogenous agonist binding site) but alter receptor conformations that influence the binding and/or functional properties of agonists binding to the orthosteric site. Compared to homomeric receptors, heteromeric receptors contain an increased number of potential allosteric sites for drug interaction.

This review examines clinically relevant allosteric modulators of 5-HT₃ receptors, and focuses on compounds that modulate 5-HT₃ receptors at physiological concentrations. The current list of compounds is based on work performed almost entirely on homomeric 5-HT_{3A} receptors. With the existence of five genes encoding for 5-HT₃ receptor subunits in the human genome, it is inevitable that the known pharmacology of the listed allosteric compounds will change when tested against novel 5-HT₃ subunit combinations.

Alcohols and volatile anesthetics

Alcohols and volatile anesthetics can produce an assortment of behavioral effects. Numerous targets have been proposed to explain the effects of alcohols and anesthetics, including the 5-HT₃ receptor. Activation of 5-HT₃ receptors enhances the release of the neurotransmitters dopamine (DA) and γ -aminobutyric acid (GABA), which are believed to be the principal neurotransmitters for addiction and intoxication respectively. 5-HT₃ receptor antagonists reduce the halothane-mediated inhibition of spinal sensory neuronal responses to noxious peripheral stimulation, indicating that 5-HT₃ receptors are anesthetic targets for the reduction in nociception [4]. In addition, 5-HT₃ receptor antagonists are used to prevent and treat PONV, which has a strong association with the use of halogenated volatile anesthetics [5], implicating a possible interaction with 5-HT₃ receptors.

For human 5-HT_{3A} receptors, currents evoked by low concentrations of 5-HT were enhanced by compounds of smaller molecular volumes (<120 Å³) such as butanol and halothane, whereas larger compounds (e.g. octanol, hexanol and sevoflurane) inhibited such currents [6]. The smaller compounds shifted the 5-HT concentration-response relationship to the left, reflecting an increase in the 5-HT_{3A} receptors' sensitivity to agonist. Compared with 5-HT_{3A} receptors, the current amplitude enhancement by butanol and pentanol was significantly less in 5-HT_{3AB} receptors with no shift in 5-HT EC₅₀ values, yet the two receptor subtypes were equally sensitive to the inhibitory action of octanol [7]. Similarly, Hayrapetyan et al. observed that, when compared to rodent 5-HT_{3A} receptors, 5-HT_{3AB} receptors were much less sensitive to the enhancing action of ethanol [8]. The smaller anesthetics and alcohols enhance the 5-HT_{3A} receptors' channel gating efficacy without altering the agonist binding affinity. Incorporation of the 5-HT_{3B} subunit reduces this enhancement of gating efficacy [9–10].

The increase in channel gating by alcohols strongly suggests that the open state of the channel has been stabilized. However, due to the low single-channel conductance of the 5-HT_{3A} receptor the direct observation of single open channels was not possible until recently. Using a triple mutant receptor (5-HT_{3A}(QDA)) that forms homomeric channels exhibiting a measurable single-channel conductance [11–12] the stability of the open channel by ethanol was confirmed (Figure 1). By examining the different open states evoked by saturating 5-HT in the absence and presence of ethanol the prolonged open state appeared to come at the expense of the desensitized state [13**]. This prolongation of the open state of the channel at the expense of the desensitized state is consistent with the slowed desensitization effect of ethanol and trichloroethanol on macroscopic currents [14–15].

Intravenous anesthetics

In comparison to the potentiation of 5-HT-evoked currents by volatile anesthetics of low molecular volume, intravenous anesthetics have an inhibitory effect on 5-HT₃ receptor

channels. Various experimental approaches such as 5-HT₃ receptor-mediated depolarizations of the rat isolated vagus nerve, currents recorded from oocytes and HEK293 cells expressing 5-HT₃ receptors or rodent cell lines with native 5-HT₃ receptors have been employed to study intravenous anesthetics modulation of 5-HT₃ receptors. In all the experimental approaches, the IC₅₀ values for barbiturate anesthetics, etomidate and propofol are significantly higher than the clinical anesthetic concentration [16–17].

At clinically relevant concentrations, the dissociative anesthetic ketamine (approximately 10 μM, [18]) has been reported to enhance 5-HT₃ receptor-mediated currents in rabbit neurons [19]. However, an inhibition at higher concentrations was also reported. Conversely, no modulation of 5-HT₃ receptor-evoked currents was observed with clinically relevant concentrations in neurons from guinea pig or from mouse 5-HT_{3A} receptors stably expressed in HEK293 cells, suggesting a species-dependent effect [20].

Antidepressants and antipsychotics

The therapeutic endpoints of antidepressants are often stated to increase the levels of neurotransmitters by various mechanisms. However, there is increasing awareness that antidepressants associate with 5-HT₃ receptors, resulting in an allosteric inhibition. Fan [21] showed in rat neurons that imipramine (tricyclic), fluoxetine (selective serotonin reuptake inhibitor, SSRI), phenelzine and iproniazid (monoamine oxidase inhibitors, MAOI) inhibit 5-HT₃ receptor-mediated currents.

At low, clinically relevant concentrations fluoxetine, imipramine and doxepin (tricyclic) inhibit 5-HT_{3A} receptors in both the open and closed conformational states with the block in the closed state resulting in a greater inhibition [22–23*]. The major metabolite of fluoxetine - norfluoxetine - is a more potent blocker than fluoxetine [22]. Fluoxetine, imipramine, phenelzine and iproniazid also accelerate desensitization [21–22].

Activation of presynaptic 5-HT₃ receptors on dopaminergic neurons of the mesolimbic system enhances dopamine release. Accordingly, antagonists of 5-HT₃ receptors may hold novel antipsychotic properties due to the dopamine hypothesis for schizophrenia. Current antipsychotic compounds have already been described to block 5-HT₃ receptors at clinically relevant concentrations. For human 5-HT_{3A} receptors expressed in HEK293 cells and endogenous receptors expressed in murine N1E-115 cells, clozapine blocked in a competitive manner but flupentixol, fluphenazine, haloperidol, levomepromazine, and thioridazine acted as allosteric inhibitors [24].

Antidepressants (desipramine, fluoxetine and reboxetine), antipsychotics (fluphenazine, haloperidol and clozapine) and 5-HT₃ receptors have been shown to co-localize in lipid raft domains. This was initially thought to imply that lipid rafts were crucial for the antagonistic properties of these compounds [25]. However, further studies have shown that disruption of lipid raft integrity altered 5-HT₃ receptor kinetics and current amplitude while block of 5-HT₃ receptors by desipramine and fluoxetine remained unaltered [26].

Cannabinoids

Both natural (Δ⁹-THC and anandamide) and synthetic (WIN55,212-2, JWH-015 and CP55940) cannabinoids have been shown to efficiently suppress nausea and vomiting and to exhibit analgesic properties [27]. However, these cannabinoid compounds have limited therapeutic potential due to their psychotropic actions mediated by their agonistic profile at cannabinoid (CB) receptors. In addition, cannabinoids inhibit 5-HT₃ receptors.

Anandamide exhibited a high potency for block of human 5-HT₃ receptors compared to its K_i for human CB1 and CB2 receptors [28]. As a possible mechanism of action for anandamide-induced block of 5-HT₃A receptors Xiong et al [29] suggested that anandamide accelerates receptor desensitization.

Recently the nonpsychotropic cannabinoid, cannabidiol, has been shown to be an allosteric inhibitor of mouse 5-HT₃A receptors [30*]. Cannabidiol's nonpsychotropic properties are explained by a very low affinity for the CB1 and CB2 receptors. However, cannabidiol still has antiemetic effects. These data demonstrate that part of the desired therapeutic endpoints of cannabinoids may be due to an allosteric inhibition of 5-HT₃ receptors.

Other compounds

A number of other compounds have been shown to modulate 5-HT₃ receptors. These include local anesthetics; lidocaine and bupivacaine which are both competitive and allosteric antagonists at the 5-HT₃A receptor [31]. Steroids are non-competitive inhibitors of 5-HT₃ receptors, but only at concentrations that exceed physiological concentrations [2*]. Morphine, hydromorphone, and fentanyl have been shown to cause a competitive block of 5-HT₃A receptors [32–33]. Methadone, an opioid often used to treat morphine addiction, also competitively inhibits human 5-HT₃A receptors and increases desensitization. However, an insurmountable block was observed for heteromeric human 5-HT₃AB receptors [34*].

In addition to the natural cannabinoid compounds mentioned above, other naturally occurring compounds are known to modulate 5-HT₃ receptors [2*]. These naturally occurring compounds include quinine, extracts from ginger, ginseng and liquorice as well as α -thujone, a component of the volatile oils from wormwood, thyme, sage. However, it is difficult to directly compare the *in vivo* concentrations of the reputed therapeutic benefits of some “traditional medicines” with the *in vitro* concentrations.

Kinetic mechanisms of 5-HT₃A receptor modulation

So how do the allosteric compounds modulate 5-HT-elicited current amplitudes and shift 5-HT concentration response curves? We have recently developed a kinetic model (Figure 2) [35] that defines agonist-evoked activation of 5-HT₃A receptors. Agonist (A) binds to the closed, resting state of the receptor (R) and the agonist-bound receptor (AR) then transitions to an open channel state (AO). From the open state the receptor can desensitize (AD) or, if the agonist is removed, can close either through the open states (A_nO) or the pre-open states (A_nR). Positive modulators may increase the 5-HT₃ receptors' sensitivity to agonist by increasing agonist binding affinity (increasing k_1/k_2), increasing channel gating efficacy (increasing β/α), or by reducing the rate of desensitization (decrease k_{d+}/k_d). Allosteric antagonists would bind to the receptor and cause opposite effects on these kinetic transitions.

Polymorphisms of 5-HT₃ receptors influence pharmacology

In recent years an increasing amount of literature has been published detailing the occurrence and influence of 5-HT₃ subunit polymorphisms in a number of pathological states. Some polymorphisms alter channel kinetics [36], which may influence the binding and/or action of allosteric compounds such that they alter the effectiveness and side effects of some therapeutic compounds. Therapeutic responses to and side effects of the SSRI paroxetine are influenced by variants in the 5-HT₃A subunit and 5-HT₃B subunit respectively [37–38]. A variant in the 5-HT₃A subunit alters the clinical response to the atypical antipsychotic risperidone in schizophrenic patients [39]. Increased potency for

clozapine block has been observed in the rare 5-HT_{3A}(P391R) variant observed in at least one schizophrenic patient [40]. It has been proposed that variants in 5-HT₃ subunits underlie treatment-resistant schizophrenia [41–43]. The area of 5-HT₃ receptor polymorphisms is a new and exciting area that may enhance our knowledge of certain pathologies and lead to novel therapies.

Future aspects

Most studies to date have been performed on homomeric 5-HT_{3A} receptors, usually performed on expressed rodent subunits and at room temperature. Rodents have only two orthologs of the five genes that encode human 5-HT₃ subunit genes. It has been noted that rodents do not make good models for gastrointestinal research [44*]. If rodents are not a good model for 5-HT₃ receptor mechanisms in the “little brain” then perhaps the rodent is an unsatisfactory model for learning about 5-HT₃ receptor physiology or potential 5-HT₃ receptor-based CNS therapies. However, humanized mice will undoubtedly expand our knowledge of the complexities of the 5-HT₃ receptor and its pharmacology. Our knowledge of heteromeric 5-HT₃ receptors is limited; we have just begun to appreciate the complexity of human 5-HT₃ receptors *in vivo* and their potential for pharmacological manipulation.

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References

1. Davies PA, Wang W, Hales TG, Kirkness EF. A novel class of ligand-gated ion channel is activated by Zn²⁺ J Biol Chem. 2003; 278:712–717. [PubMed: 12381728]
- *2. Walstab J, Rappold G, Niesler B. 5-HT₃ receptors: role in disease and target of drugs. Pharmacol Ther. 2010; 128:146–169. This review is a comprehensive review on 5-HT₃ receptors covering genetics, pathology and pharmacology. It contains an updated review of competitive antagonists. [PubMed: 20621123]
3. Thompson AJ, Lummis SC. The 5-HT₃ receptor as a therapeutic target. Expert Opin Ther Targets. 2007; 11:527–540. [PubMed: 17373882]
4. Koshizaki M, Kawamata M, Shimada SG, Saito Y, Collins JG. 5-HT₃ receptors partially mediate halothane depression of spinal dorsal horn sensory neurons. Anesth Analg. 2003; 96:1027–1031. [PubMed: 12651653]
5. Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, Heineck R, Greim CA, Roewer N. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth. 2002; 88:659–668. [PubMed: 12067003]
6. Stevens RJ, Rusch D, Davies PA, Raines DE. Molecular properties important for inhaled anesthetic action on human 5-HT_{3A} receptors. Anesth Analg. 2005; 100:1696–1703. [PubMed: 15920198]
7. Stevens R, Rusch D, Solt K, Raines DE, Davies PA. Modulation of human 5-hydroxytryptamine type 3AB receptors by volatile anesthetics and n-alcohols. J Pharmacol Exp Ther. 2005; 314:338–345. [PubMed: 15831437]
8. Hayrapetyan V, Jenschke M, Dillon GH, Machu TK. Co-expression of the 5-HT_{3B} subunit with the 5-HT_{3A} receptor reduces alcohol sensitivity. Brain Res Mol Brain Res. 2005; 142:146–150. [PubMed: 16257471]
9. Solt K, Stevens RJ, Davies PA, Raines DE. General anesthetic-induced channel gating enhancement of 5-hydroxytryptamine type 3 receptors depends on receptor subunit composition. J Pharmacol Exp Ther. 2005; 315:771–776. [PubMed: 16081679]

10. Rusch D, Musset B, Wulf H, Schuster A, Raines DE. Subunit-dependent modulation of the 5-hydroxytryptamine type 3 receptor open-close equilibrium by n-alcohols. *J Pharmacol Exp Ther*. 2007; 321:1069–1074. [PubMed: 17360702]
11. Kelley SP, Dunlop JI, Kirkness EF, Lambert JJ, Peters JA. A cytoplasmic region determines single-channel conductance in 5-HT₃ receptors. *Nature*. 2003; 424:321–324. [PubMed: 12867984]
12. Hales TG, Dunlop JI, Deeb TZ, Carland JE, Kelley SP, Lambert JJ, Peters JA. Common determinants of single channel conductance within the large cytoplasmic loop of 5-hydroxytryptamine type 3 and $\alpha 4\beta 2$ nicotinic acetylcholine receptors. *J Biol Chem*. 2006; 281:8062–8071. [PubMed: 16407231]
- **13. Feinberg-Zadek PL, Davies PA. Ethanol stabilizes the open state of single 5-hydroxytryptamine(3A)(QDA) receptors. *J Pharmacol Exp Ther*. 2010; 333:896–902. This study used a high conducting mutant 5-HT₃A subunit that allowed for the study of ethanol modulation 5-HT₃A receptors at a single channel level. [PubMed: 20200118]
14. Zhou Q, Verdoorn TA, Lovinger DM. Alcohols potentiate the function of 5-HT₃ receptor-channels on NCB-20 neuroblastoma cells by favouring and stabilizing the open channel state. *J Physiol*. 1998; 507:335–352. [PubMed: 9518697]
15. Hu XQ, Sun H, Peoples RW, Hong R, Zhang L. An interaction involving an arginine residue in the cytoplasmic domain of the 5-HT₃A receptor contributes to receptor desensitization mechanism. *J Biol Chem*. 2006; 281:21781–21788. [PubMed: 16754678]
16. Barann M, Linden I, Witten S, Urban BW. Molecular actions of propofol on human 5-HT₃A receptors: enhancement as well as inhibition by closely related phenol derivatives. *Anesth Analg*. 2008; 106:846–857. [PubMed: 18292429]
17. Rusch D, Braun HA, Wulf H, Schuster A, Raines DE. Inhibition of human 5-HT(3A) and 5-HT(3AB) receptors by etomidate, propofol and pentobarbital. *Eur J Pharmacol*. 2007; 573:60–64. [PubMed: 17669396]
18. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. *Br J Anaesth*. 1983; 55:1107–1111. [PubMed: 6639827]
19. Peters JA, Malone HM, Lambert JJ. Ketamine potentiates 5-HT₃ receptor-mediated currents in rabbit nodose ganglion neurones. *Br J Pharmacol*. 1991; 103:1623–1625. [PubMed: 1718520]
20. Yamakura T, Chavez-Noriega LE, Harris RA. Subunit-dependent inhibition of human neuronal nicotinic acetylcholine receptors and other ligand-gated ion channels by dissociative anesthetics ketamine and dizocilpine. *Anesthesiology*. 2000; 92:1144–1153. [PubMed: 10754635]
21. Fan P. Effects of antidepressants on the inward current mediated by 5-HT₃ receptors in rat nodose ganglion neurones. *Br J Pharmacol*. 1994; 112:741–744. [PubMed: 7522857]
22. Choi JS, Choi BH, Ahn HS, Kim MJ, Rhie DJ, Yoon SH, Min DS, Jo YH, Kim MS, Sung KW, et al. Mechanism of block by fluoxetine of 5-hydroxytryptamine₃ (5-HT₃)-mediated currents in NCB-20 neuroblastoma cells. *Biochem Pharmacol*. 2003; 66:2125–2132. [PubMed: 14609737]
- *23. Gumilar F, Bouzat C. Tricyclic antidepressants inhibit homomeric Cys-loop receptors by acting at different conformational states. *Eur J Pharmacol*. 2008; 584:30–39. This study used the high conducting 5-HT₃A subunit mutant to demonstrate that tricyclic antidepressants inhibit through both open and closed states. The study also examined the block at a single-channel level. [PubMed: 18314100]
24. Rammes G, Eisensamer B, Ferrari U, Shapa M, Gimpl G, Gilling K, Parsons C, Riering K, Hapfelmeier G, Bondy B, et al. Antipsychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner. *Mol Psychiatry*. 2004; 9:846–858. 818. [PubMed: 15024394]
25. Eisensamer B, Uhr M, Meyr S, Gimpl G, Deiml T, Rammes G, Lambert JJ, Zieglgansberger W, Holsboer F, Rupprecht R. Antidepressants and antipsychotic drugs colocalize with 5-HT₃ receptors in raft-like domains. *J Neurosci*. 2005; 25:10198–10206. [PubMed: 16267227]
26. Nothdurfter C, Tanasic S, Di Benedetto B, Rammes G, Wagner EM, Kirmeyer T, Ganai V, Kessler JS, Rein T, Holsboer F, et al. Impact of lipid raft integrity on 5-HT₃ receptor function and its modulation by antidepressants. *Neuropsychopharmacology*. 2010; 35:1510–1519. [PubMed: 20200506]

27. Pertwee RG. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *Br J Pharmacol.* 2009; 156:397–411. [PubMed: 19226257]
28. Barann M, Molderings G, Bruss M, Bonisch H, Urban BW, Gothert M. Direct inhibition by cannabinoids of human 5-HT_{3A} receptors: probable involvement of an allosteric modulatory site. *Br J Pharmacol.* 2002; 137:589–596. [PubMed: 12381672]
29. Xiong W, Hosoi M, Koo BN, Zhang L. Anandamide inhibition of 5-HT_{3A} receptors varies with receptor density and desensitization. *Mol Pharmacol.* 2008; 73:314–322. [PubMed: 17993512]
- *30. Yang KH, Galadari S, Isaev D, Petroianu G, Shippenberg TS, Oz M. The nonpsychoactive cannabinoid cannabidiol inhibits 5-hydroxytryptamine_{3A} receptor-mediated currents in *Xenopus laevis* oocytes. *J Pharmacol Exp Ther.* 2010; 333:547–554. This study demonstrates that the non-psychotropic, analgesic and antiemetic cannabinoid, cannabidiol (CBD) is an allosteric inhibitor of 5-HT₃ receptors. This raises the possibility that some of the therapeutic benefits of cannabinoids maybe through the 5-HT₃ receptor and that allosteric modulators of 5-HT₃ receptors show useful therapeutic potential. [PubMed: 20160007]
31. Ueta K, Suzuki T, Sugimoto M, Uchida I, Mashimo T. Local anesthetics have different mechanisms and sites of action at recombinant 5-HT₃ receptors. *Reg Anesth Pain Med.* 2007; 32:462–470. [PubMed: 18035290]
32. Wittmann M, Peters I, Schaaf T, Wartenberg HC, Wirz S, Nadstawek J, Urban BW, Barann M. The effects of morphine on human 5-HT_{3A} receptors. *Anesth Analg.* 2006; 103:747–752. [PubMed: 16931691]
33. Wittmann M, Schaaf T, Peters I, Wirz S, Urban BW, Barann M. The effects of fentanyl-like opioids and hydromorphone on human 5-HT_{3A} receptors. *Anesth Analg.* 2008; 107:107–112. [PubMed: 18635474]
- *34. Deeb TZ, Sharp D, Hales TG. Direct subunit-dependent multimodal 5-hydroxytryptamine₃ receptor antagonism by methadone. *Mol Pharmacol.* 2009; 75:908–917. This study further demonstrates how subunit composition of the receptor can alter 5-HT₃ receptor pharmacology. [PubMed: 19131665]
35. Solt K, Ruesch D, Forman SA, Davies PA, Raines DE. Differential effects of serotonin and dopamine on human 5-HT_{3A} receptor kinetics: interpretation within an allosteric kinetic model. *J Neurosci.* 2007; 27:13151–13160. [PubMed: 18045909]
36. Krzywkowski K, Davies PA, Feinberg-Zadek PL, Brauner-Osborne H, Jensen AA. High-frequency HTR3B variant associated with major depression dramatically augments the signaling of the human 5-HT_{3AB} receptor. *Proc Natl Acad Sci U S A.* 2008; 105:722–727. [PubMed: 18184810]
37. Kato M, Fukuda T, Wakeno M, Fukuda K, Okugawa G, Ikenaga Y, Yamashita M, Takekita Y, Nobuhara K, Azuma J, et al. Effects of the serotonin type 2A, 3A and 3B receptor and the serotonin transporter genes on paroxetine and fluvoxamine efficacy and adverse drug reactions in depressed Japanese patients. *Neuropsychobiology.* 2006; 53:186–195. [PubMed: 16874005]
38. Sugai T, Suzuki Y, Sawamura K, Fukui N, Inoue Y, Someya T. The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. *Pharmacogenomics J.* 2006; 6:351–356. [PubMed: 16534507]
39. Gu B, Wang L, Zhang AP, Ma G, Zhao XZ, Li HF, Feng GY, He L, Xing QH. Association between a polymorphism of the HTR3A gene and therapeutic response to risperidone treatment in drug-naïve Chinese schizophrenia patients. *Pharmacogenet Genomics.* 2008; 18:721–727. [PubMed: 18622264]
40. Rammes G, Hosp C, Eisensamer B, Tanasic S, Nothdurfter C, Zieglgansberger W, Rupprecht R. Identification of a domain which affects kinetics and antagonistic potency of clozapine at 5-HT₃ receptors. *PLoS One.* 2009; 4:e6715. [PubMed: 19696922]
41. Ji X, Takahashi N, Branko A, Ishihara R, Nagai T, Mouri A, Saito S, Maeno N, Inada T, Ozaki N. An association between serotonin receptor 3B gene (HTR3B) and treatment-resistant schizophrenia (TRS) in a Japanese population. *Nagoya J Med Sci.* 2008; 70:11–17. [PubMed: 18807291]
42. Ji X, Takahashi N, Saito S, Ishihara R, Maeno N, Inada T, Ozaki N. Relationship between three serotonin receptor subtypes (HTR3A, HTR2A and HTR4) and treatment-resistant schizophrenia in the Japanese population. *Neurosci Lett.* 2008; 435:95–98. [PubMed: 18359159]

43. Meineke C, Tzvetkov MV, Bokelmann K, Oetjen E, Hirsch-Ernst K, Kaiser R, Brockmoller J. Functional characterization of a -100_-102delAAG deletion-insertion polymorphism in the promoter region of the HTR3B gene. *Pharmacogenet Genomics*. 2008; 18:219–230. [PubMed: 18300944]
- *44. Holbrook JD, Gill CH, Zebda N, Spencer JP, Leyland R, Rance KH, Trinh H, Balmer G, Kelly FM, Yusuf SP, et al. Characterisation of 5-HT₃C, 5-HT₃D and 5-HT₃E receptor subunits: evolution, distribution and function. *J Neurochem*. 2009; 108:384–396. Study examining the function of 5-HT₃ receptors containing 5-HT₃C, 5-HT₃D and 5-HT₃E subunits. Discusses the potential importance of these subunits to human physiology and the difficulty of using rodents to study 5-HT₃ receptors due to the lack of genes encoding these subunits. [PubMed: 19012743]

Figure 1. Ethanol increases the number of open single-channel events

Left, Cell-attached recordings of human 5-HT₃A(QDA)-mediated currents evoked by 100 μM 5-HT in the absence (**A**) or presence (**B**) of 25 mM ethanol. Twenty second examples of single-channel activity with an expanded view of a burst (left panel). Dotted lines indicating closed and open states. Right, all-points histograms for the 20 s recordings of 5-HT₃A(QDA)-mediated currents evoked by 100 μM 5-HT shown in left panel. Histograms were fitted by two Gaussians, percentages of events in the closed and open states are shown. Figure reproduced, with permission, from Feinberg-Zadek and Davies [13].

Figure 2. Kinetic model of 5-HT_{3A} receptor function

The major states and transitions required to account for the actions of agonists on 5-HT₃ receptors are shown in black. The minor transitions, which are shown in grey, are assumed to be possible, but negligible. Values of rate constants (denoted above and below arrows) determined from macroscopic current experiments with rapid solution exchange are given in Solt et al. [40].