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Commentary

The action of aripiprazole and brexpiprazole at the receptor level in *singultus*

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The hiccup (Latin *singultus*) is an involuntary periodic contraction of the diaphragm followed by glottic closure, which can be a rare side effect of aripiprazole. In contrast to the structurally closely related aripiprazole, brexpiprazole was not associated with this particular adverse drug reaction. Having two very similar drugs that differ in their ability to induce hiccups represents a unique opportunity to gain insight into the receptors involved in the pathophysiology of the symptom and differences in clinical effects between aripiprazole and brexpiprazole. The overlap between maneuvers used to terminate paroxysmal supraventricular tachycardia and those employed to terminate bouts of hiccups suggests that activation of efferent vagal fibers can be therapeutic in both instances. Recent work seems to support a pivotal role for serotonin receptors in such vagal activation. It is unlikely that a unique receptor-drug interaction could explain the different effects of the examined drugs on hiccup. The different effect is most likely the consequence of several smaller effects at more than one receptor. Brexpiprazole is a highly affine (potent) α_{2C} antagonist and, therefore, also an indirect 5-HT$_{1A}$ agonist. In contrast, aripiprazole is a partial 5-HT$_{1A}$ agonist (weak antagonist) and an HT$_3$ antagonist. Activation of 5-HT$_{1A}$ receptors enhances vagal activity while HT$_3$ blockade reduces it. Vagus nerve activation is therapeutic for hiccups. A definitive answer continues to be elusive.

Keywords

Neuropharmacology; Hiccup; Serotonin; Aripiprazole; Brexpiprazole; Affinity constant

1. Introduction

Hiccup (Latin, *singultus*) is caused by an involuntary periodic contraction of the diaphragm followed by the glottis's closure. The inspired air meeting a closed glottis causes the familiar hiccup sound. Hiccupping lasting longer than four weeks is considered chronic. Treatment resistance (obstinate hiccup) is defined as a lack of response to many (mostly three) successive pharmacological treatments attempt. Generally, the longer the hiccupping duration, the less amenable it will be to interventions [1].

Singultus is not a disease but a symptom. The most commonly encountered hiccup is that of idiopathic origin. While many drugs have been tried off-label in hiccup therapy, chlorpromazine is the only FDA approved drug for this purpose. In contrast, only a few drugs (benzodiazepines, barbiturates, alcohol, and steroids) and the phenyl-piperazine atypical antipsychotic aripiprazole are well-established hiccup inducers [1].

Since the initial observation made by Behere [2] that aripiprazole can induce hiccups (in his case, associated with hyponatremia), an abundance of reports on hiccups associated with aripiprazole treatment emerged [3–11], and on persistent hiccups associated with switching antipsychotic treatment to aripiprazole [12–15].

More recently, brexpiprazole was introduced into clinical practice [16]. In contrast to the structurally closely related aripiprazole, brexpiprazole was not associated with this particular adverse drug reaction. Having two very similar drugs that differ in their ability to induce hiccup represents a unique opportunity to gain insight into the receptors involved in the symptom's pathophysiology.

To identify the critical difference responsible for the discrepancy, we performed a literature search (PubMed and public domain sources) and retrieved and compared the PK/PD data and properties of the two piperazine antipsychotics at serotoninergic, alpha$_2$-adrenergic and dopaminergic receptors.

While aware of the limitations of comparing receptor affinities/intrinsic activity values-even more so when obtained from different sources using different methodologies-(as they have considerable confidence intervals) and inferring biological effects based on such data, it is currently the only practical available option for our analysis [17, 18].

2. Methods

To identify the critical difference responsible for the discrepancy, a literature search (PubMed and public domain sources) was performed, and pharmacokinetics and pharmacodynamic (PK/PD) data/properties of the two piper-

azine antipsychotics at serotoninergic alpha$_2$-adrenergic and dopaminergic receptors retrieved and compared. Due to the limited number of publications containing pharmacokinetic and or pharmacodynamic details on aripiprazole and brexpiprazole, no filters were applied.

As a matter of terminology -as used by us-when comparing K_i values of the two drugs, very (strong) high affinity implies subnanomolar K_i values, high-affinity K_i between 1 and 10 nM, moderate K_i between 10 and 50 nM, low affinity is K_i between 50 and 100 nM and very (weak) low affinity for K_i higher than 150 nM. For K_i values above 90% of the therapeutic plasma range (700 nM for aripiprazole and 300 nM for brexpiprazole), no effect via the respective receptor is assumed. The inhibition constant (K_i) is calculated based on the following: $K_i = IC_{50}$ for noncompetitive inhibition, $K_i = IC_{50}/2$ for competitive inhibition, and K_i values range from IC_{50} to $IC_{50}/2$ for mixed inhibition, according to the equation [19]: $K_i = IC_{50}/(1 + ([L]/Kd)$ where [L] is the concentration of ligand (nM), and Kd is the affinity constant (nM).

For comparison purposes K_i ratios are given as K_i aripiprazole/K_i brexpiprazole, i.e., $[K_i(^{ARI}/_{BREX})]$; a value > 1 indicates lower affinity of aripiprazole for the respective receptor while a value < 1 indicates higher affinity of aripiprazole for the respective receptor. Divergent or significantly different effects are assumed when the ratio is either $> 10^2$ or $<$ then 10^{-2}. The same applies when only one of the drugs has a K_i within the therapeutic range [22]. K_i is used to describing the binding affinity that a molecule has for an enzyme or receptor. The half-maximal inhibitor concentration IC_{50} is more reflective of the inhibitor's functional strength, but both factors in the drug's concentration inhibit the activity. Efficacy is the relationship between receptor occupancy and the ability to initiate a response. As a matter of terminology -as used by us-when comparing K_i (binding affinity constant) values of the two drugs, very (strong) high affinity implies subnanomolar K_i values, high-affinity K_i between 1 and 10 nM, moderate K_i between 10 and 50 nM. Low affinity is K_i between 50 and 100 nM and very (weak) low affinity for K_i higher than 150 nM. For K_i values above 90% of the therapeutic plasma range (700 nM for aripiprazole and 300 nM for brexpiprazole), no effect via the respective receptor is assumed because such supratherapeutic (possibly toxic) levels are not clinically targeted.

The daily dose range for aripiprazole (MW 448) is 10-30 mg with a dose-dependent therapeutic plasma range of 100-350 (ng/mL) [223-780 nM]; for the more potent brexipirazole (MW 434), the daily dose range is 2-4 mg with a (dose-dependent) therapeutic plasma range of 40-140 (ng/mL) [92-323 nM] [20]. For K_i values above 90% of the therapeutic plasma range (700 nM for aripiprazole and 300 nM for brexpiprazole), no effect via the respective receptor is assumed.

The brain aripiprazole concentration is approximately 0.6-0.9 of the respective plasma concentrations [21], while brexpiprazole is 0.2-0.4[1]. These ratios are difficult to interpret, as they do not compare C_{max} plasma with C_{max} brain.

The abstracts of the 60 documents (search 2 and 4) were evaluated by two of the authors (GAP & EA) for the likelihood the paper containing relevant pharmacokinetic and pharmacodynamics (pK/pD) data (affinity, IC_{50}, EC_{50}, receptor occupancy). The consensus papers were mined for the targeted data. To complement the information thus obtained, a series of databases and other public domain publications (European Medicines Agency (EMA), 2018; Drugs FDA; Lundbeck; American Psychiatric Association; PubChem Database) were also consulted. Sources are cited wherever they are used.

3. Results

3.1 Serotonin (5-HT) receptors

5-HT$_{1A}$ (K_i 5-HT ≈ 2): Brexpiprazole, despite an affinity one order of magnitude higher ($[K_i(^{ARI}/_{BREX})] \approx 1.7/0.12 \approx 14$) than aripiprazole, displayed comparable receptor occupancy and an only slightly lower efficacy [Emax expressed as a percentage of the effect of serotonin = 0.6_{BREX} vs. 0.7_{ARI}] [23]. Both drugs are less efficacious than the endogenous neurotransmitter serotonin ($E_{max} \approx 1$), thus acting as partial agonists. The two drugs have very similar effects via this receptor, even though some argue that brexpiprazole is a full 5-HT$_{1A}$ receptor agonist [24, 25] (Table 1).

5-HT$_{1B}$ (K_i 5-HT ≈ 4): While aripiprazole is unlikely to significantly affect this receptor (K_i outside of the therapeutic range, brexpiprazole will act as an antagonist. One can speculate that brexpiprazole as an antagonist will have some vasodilating effect (Table 1).

5-HT$_{2A}$ (K_i 5-HT ≈ 12): The effects of brexpiprazole and aripiprazole at 5-HT$_{2A}$ are measured via studying DOI-(2,5-dimethoxy-4-iodoamphetamine)-induced head twitches (mediated via 5-HT$_{2A}$): brexpiprazole and aripiprazole inhibited DOI-induced head twitches; maximum responses (Mean ± S.E.M.) for brexpiprazole and aripiprazole were; 99 ± 0.9, and 91 ± 3.6, respectively. Brexpiprazole, despite an affinity about one order of magnitude higher ($[K_i(^{ARI}/_{BREX})] \approx 3.4/0.47 \approx 7$) than aripiprazole, displayed comparable 2A receptor occupancy [23]. As with all atypical antipsychotics, both drugs act at this receptor as antagonists. The two drugs have similar effects via this receptor [26]. Thus, it is unlikely that interaction with this receptor might explain the different ADR profile of the two drugs (Table 1).

5-HT$_{2B}$ (K_i 5-HT ≈ 9): Brexpiprazole, despite a lower 2B affinity than aripiprazole ($[K_i(^{ARI}/_{BREX})] \approx 0.36/1.9 \approx 0.2$) displayed comparable $IC_{50} \approx$ 10-15 nM [16, 23, 27].

[1] ABILIFY® A. Bristol-Myers Squibb Company. U.S. Food and Drug Administration website Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021713s004,021436s007lbl.pdf (Accessed: 07 May 2020)

Table 1. The affinity ratio between Aripiprazole and Brexpiprazole $K_i(^{ARI}/_{BREX})$ and effect at different serotonin receptors and transporter.

	ARI Therapeutic Range **223-780 nM**	**BREX** Therapeutic Range **92-323 nM**		
	K_i ARI nM	**K_i BREX nM**	**$K_i(^{ARI}/_{BREX})$**	**Effect**
5-HT_{1A}	1.3 [23]	0.12 [23]	14	partial agonism
5-HT_{1B}	830 [27]	32 [23]	26	antagonism
5-HT_{1D}	68 [27]	Not available		
5-HT_{1E}	8000 [27]	Not available		
5-HT_{2A}	4.7 [23]	0.47 IC_{50} 6.5 [23]	10	antagonism
5-HT_{2B}	0.36 [58]	1.9 [23]	0.2	antagonism/inverse agonism
5-HT_{2C}	15 [27]	34 [27]	0.4	antagonism
5-H_{T3}	630 [27]	Not available		Possiblydivergent; only ARI
5-H_{T5}	1240 [27]	140[1]	8.9	possibly divergent; only BREX
5-H_{T6}	570 [27] 219 [59]	60 [23]	3.6 -9.5	weak antagonism
5-H_{T7}	39 [27]	3.7 [23]	10	weak partial agonism
SERT[a] [a]: serotonin transporter	95 (IC_{50})	29 (IC_{50})	3.3 [IC_{50} ($^{ARI}/_{BREX}$)]	inhibition

[1] Committee for Medicinal Products for Human Use. Rxulti (Brexpiprazole) Assessment report. 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/rxulti-epar-public-assessment-report_en.pdf.

While K_i is used to describing the binding affinity that a molecule has for an enzyme or receptor.

The half-maximal inhibitory concentration IC_{50} is more reflective of the inhibitor's functional strength, but both factors in the drug's concentration inhibit the activity. The drugs act at this receptor as antagonists/inverse agonists and have similar effects via this receptor. Thus, it is unlikely that interaction with this receptor might explain the different ADR profile of the two drugs (Table 1).

5-HT_{2C} (K_i 5-HT $\approx$ 5): Binding affinity of brexpiprazole at the 2C receptor was lower than that of aripiprazole: $[K_i(^{ARI}/_{BREX})] \approx 15/34 \approx 0.4$. Despite that, the two drugs showed similarly low efficacies ($E_{max} \approx 10\%$) compared with serotonin. Both drugs act as weak partial agonists, de facto antagonists [26, 27] (Table 1).

5-HT_3 (K_i 5-HT $\approx$ 200): K_i of aripiprazole at this receptor is K_i 630 $\pm$ 110 nM [27]. In comparison the endogenous agonist 5-HT has a K_i = 200 nM [28]. No data for brexpiprazole could be found, nor any indication that the drug would interact with this receptor. Only aripiprazole likely has a week effect mediated via this receptor (Table 1).

5-HT_4 (K_i 5-HT $\approx$ 120): There is no available data suggesting any effect of the two drugs via this receptor.

5-HT_5 (K_i 5-HT $\approx$ 200): Binding affinity of aripiprazole at this receptor is negligible with a $K_i \approx 1.240 \pm 280$ nM, above the upper limit of the therapeutic plasma range [27]. Brexpiprazole $K_i \approx 140$ nM[2]. The only brexpiprazole likely has an effect mediated by this receptor (Table 1).

5-HT_6 (K_i 5-HT $\approx$ 65): K_i of aripiprazole ≈ 214 (reported range from 161 $\pm$ 17 [29] to 570 $\pm$ 95 nM [27, 29] and 780 [30]). The affinity of the weak antagonist brexpiprazole is similar to that of serotonin (58 nM), but the receptor occupancy is low at 20-40%. $K_i(^{ARI}/_{BREX}) \approx 3.5$. Both drugs act as weak antagonists (Table 1).

5-HT_7 (K_i 5-HT $\approx$ 2-8): The affinity of the endogenous agonist serotonin for the 5-HT_7 receptor is (strong) high

[2] REXULTI® B. Otsuka and Lundbeck. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205422Orig1Orig2s000PharmR.pdf (Accessed: 13 May 2020)

Table 2. The affinity ratio between Aripiprazole and Brexpiprazole $K_i(^{ARI}/_{BREX})$ and effect at adrenergic α_2 receptors and transporter.

	K_i ARI nM	K_i BREX nM	$K_i(^{ARI}/_{BREX})$	Effect
α_{2A}	74 [30]	15 [23]	5	antagonism
α_{2B}	100 [30]	17 [23]	6	antagonism
α_{2C}	37 [30]	0.59 IC_{50} 63 [23]	63	antagonism

[31, 32]. Aripiprazole, a very weak partial agonist with an $E_{max} < 10\%$ (of 5-HT effect), has a $K_i \approx 39$ nM and a receptor occupancy in the 15-30% range [27, 31, 33]. Brexpiprazole, a weak partial agonist, has a K_i of 3.7 nM and a receptor occupancy in the 10-56% range[3] [34]. $K_i(^{ARI}/_{BREX}) \approx 10$ (Table 1).

At the 5-HT_7 receptor, while aripiprazole has a (weaker) lower affinity than brexpiprazole, both drugs have similar effects (weak partial agonist, de facto antagonist) [26] (Table 1).

SERT (K_i 5-HT $\approx$ 500) [35]: Aripiprazole has an IC_{50} for the serotonin transporter $\approx$ 95 nM. Brexpiprazole is a SERT inhibitor with an IC_{50} of 29 nM but a low ligand displacement ability (65% at 10 μM)[2] (Table 1).

3.2 Alpha $_2$ (α_2) adrenergic receptors

Brexpiprazole is a highly affine α_2 adrenergic receptor antagonist [α_{2A} K_i 15 nM; α_{2B} K_i 17 nM; α_{2C} K_i 0.59 nM] comparable to mirtazapine (α_{2A} K_i 20 nM; α_{2B} K_i 88 nM; α_{2C} K_i 18 nM) [23, 30]. Aripiprazole has a slightly lower affinity for α_2 adrenergic receptors (α_{2A} K_i 74 nM; α_{2B} K_i 100 nM; α_{2C} 37 nM) [30]. K_i $(^{ARI}/_{BREX})$ for the α_2-adrenergic receptors is $\alpha_{2A} \approx 5$; for $\alpha_{2B} \approx 6$ while for $\alpha_{2C} \approx 63$. Brexpiprazole has an IC_{50} of 63 nM at α_{2C} receptors [23] (Table 2).

3.3 Dopamine (DA) receptors

D_1 (K_i DA $\approx$ 2-8): Aripiprazole has a $K_i \approx 265$ nM (reported range 200-2500 nM) [19, 27, 29]; brexpiprazole has a $K_i \approx 150$[2]. $K_i(^{ARI}/_{BREX}) \approx 265/160 \approx 1.7$. Both drugs have similar agonist effects [36, 37] (Table 3).

D_5 (K_i DA $<$ 2): Aripiprazole has a $K_i \approx 2590 \pm 1350$ nM, well above the upper limit of the therapeutic plasma range [27]. Similar values [$K_i \approx 1.670$ nM] have been reported by [38]. For brexpiprazole receptor, occupancy is $\approx$ 66% at 1 mM (Table 3).

D_2 (K_i DA $\approx 12 \pm 4$) [39]: Aripiprazole, a partial agonist with an Emax $\approx$ 60% (of D effect), has a $K_i \approx 0.32$ nM. Brexpiprazole, also a partial agonist, has a K_i 0.3 nM and an Emax $\approx$ 43%. $K_i(^{ARI}/_{BREX}) \approx 1$. At the D_2 receptor, both drugs have similar effects (partial agonist) (Table 3).

D_3 (K_i DA $\approx 3 \pm 1$) [39]: Aripiprazole, a partial agonist with an Emax $\approx$ 30% (of DA effect), has a $K_i \approx 0.8$ nM. Brexpiprazole, a weak partial agonist, has a comparable affinity ($K_i \approx 1.1$) but a lower intrinsic activity Emax $\approx$ 15%. $K_i(^{ARI}/_{BREX}) \approx 0.8$. At the D_3 receptor, while both drugs have qualitatively similar effects (partial agonist), aripiprazole has a somewhat higher intrinsic activity [26] (Table 2).

D_4 (K_i DA $\approx 6 \pm 2$) [39]: Aripiprazole has a $K_i \approx 44$ nM and an Emax of 20-30% [40]. Brexpiprazole has a higher affinity $K_i \approx 6$ nM. $K_i(^{ARI}/_{BREX}) \approx 7$. Both drugs have a partial agonist effect at this receptor (Table 3).

DAT (K_i DA $\approx 29 \pm 4$) [41]: Brexpiprazole is a negligible inhibitor of the dopamine transporter with a reported $IC_{50} \approx$ 950 nM, well above the upper limit of the therapeutic plasma range; the same applies for aripiprazole ($K_i \approx 3220 \pm 660$) [27] (Table 3).

4. Discussion

To identify differences that might explain the differential effect of the two drugs on hiccup, the affinities of aripiprazole and brexpiprazole for the various serotoninergic, alpha$_2$-adrenergic and dopaminergic receptors, as well as the respective transporters, were compared. The drugs are very similar in their pharmacodynamics at most receptors. They are generally considered partial agonists at 5-HT_{1A} and D_2 receptors and antagonists at the 5-HT_{2A} receptors; brexpiprazole has a somewhat lower intrinsic activity at the D_2 receptor and acts as a more potent 5-HT_{1A} agonist and as a stronger 5-HT_{2A} antagonist [17]. Furthermore, both drugs appear to have additional characteristics beyond partial agonist at D2 receptors, including biased agonism [42, 43]. The term biased agonism (functional selectivity), initially introduced in [44], describes the phenomenon that a ligand preferentially activates one of several signaling pathways. In contrast, another agonist in the same system and acting on the same receptor preferentially activates another pathway.

Both are dopamine system stabilizers, i.e., to have either an agonist or antagonist effect depending on the levels of exogenous dopamine (antagonist at high dopamine concentration vs. agonist at low dopamine concentration [42, 45]). Aripiprazole and brexpiprazole function as both a presynaptic D_2 agonist and postsynaptic D_2 antagonist; furthermore, their partial agonistic activity 5-HT_{1A} receptor plays a role in modulating among other dopamine releases reviewed by [42]. Effects mediated via the major psychosis relevant receptors (5-HT_{1A}, 5-HT_2 and D_2) are similar and do not provide in our view the explanation for the appearance of a hiccup with aripiprazole treatment.

Different effects appear possible at the 5-HT_3 receptor where aripiprazole has a K_i within the therapeutic plasma concentration and the 5-HT_{1B}- and 5-HT_5 receptor where brexpiprazole has a $K_i$within the therapeutic plasma concentration.

[3] Committee for Medicinal Products for Human Use. Rxulti (Brexpiprazole) Assessment report [Internet]. 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/rxulti-epar-public-assessment-report_en.pdf.

Table 3. The affinity ratio between Aripiprazole and Brexpiprazole and effect at different dopamine receptors and transporter.

	K_i (ARI) nM	K_i (BREX) nM	$K_i(^{ARI}/_{BREX})$ nM	Effect
D1	1960 [27]	160[1]	265/160 ≈ 1.7	agonism
D5	2590 [27]		2590/↑↑↑	no effect
D2	0.32 [60]	0.3 [23]	0.34/0.3 ≈ 1	partial agonism
D3	0.8-1.6 [23, 39]	1.1 [23]	0.8/1.1 ≈ 0.8	partial agonism
D4	44 [61]	6[1]	44/6 ≈ 7	partial agonism
DAT[a]	3220 [27]	950 [23]	3.220/950 ≈ 3.4	no effect

[a]: dopamine transporter

[1]Committee for Medicinal Products for Human Use. Rxulti (Brexpiprazole) Assessment report. 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/rxulti-epar-public-assessment-report_en.pdf.

5-HT$_3$ receptors are the only ionotropic serotonin receptors. 5-HT$_3$ receptors are located (mainly) on sensory vagal nerve endings and play a vital role for vagal afferent input originating from organs cranial to the Cannon-Böhm-point (the gastrointestinal tract fewer parts of the colon and rectum, lungs and heart). The central terminals of vagal afferents exhibit 5-HT$_3$ receptors that increase glutamatergic synaptic transmission to second-order neurons of the nucleus tractus solitarius [46]. Experimental compounds with 5-HT$_3$ blocking properties increase the heart rate by decreasing vagal afferent input and efferent output; this is compatible with data showing that 5-HT$_3$ receptors excite vagal afferent neurons by a glutamate-dependent mechanism [47, 48]. Blockade of these receptors by 5-HT$_3$ antagonists (setrons) is used clinically for control of emesis.

A single anecdotal mentioning of the negative impact of setrons on a patient with chronic hiccup was published by one of the authors (GAP) [49]. Some anecdotal reports claim that setrons cause hiccups [4] [5], but overall, the evidence is relatively sparse.

The possibility of aripiprazole affecting this receptor (while the same does not apply to brexpiprazole) is nevertheless intriguing as-if confirmed experimentally- it might explain their differential effect on hiccup. Mechanistically an inhibition of this receptor would be expected to lower vagal efferent output, which is believed to favor hiccup development [50].

5-HT$_5$ receptors (Gi protein-coupled) are virtually unexplored due to a lack of selective ligands [51]. As Glennon [52] points out, "*the discovery of a therapeutically useful function for the receptors*" is still outstanding. The possibility that brexpiprazole might affect this receptor (while the same does not apply for aripiprazole) cannot be inferred much at this point.

5-HT$_{1B}$ receptors (Gi protein-coupled) are the traditional target of the triptan class of drugs. Triptans act as agonists at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors at blood vessels and nerve endings in the brain and induce vasoconstriction. The only brexpiprazole has a K_i within the therapeutic range (antagonist; vasodilation). The significance or lack thereof is difficult to interpret.

Overall, we failed to identify the one receptor that might explain the different effect of the examined drugs on hiccup; it appears likely that the different effect is the consequence of synergism of several smaller effects at more than one receptor. The most consequential concerning neurotransmitter release is the central alpha$_2$ adrenergic receptor.

Brexpiprazole, similar to mirtazapine, is a highly affine α_2 antagonist [α_{2A} K_i 15 nM; α_{2B} K_i 17 nM; α_{2C} 0.59 nM] [17]. Antagonism of the α_2- receptors, which function mainly as inhibitory autoreceptors and heteroreceptors, enhances transmitter release and favors neurotransmission, notably central 5-HT$_{1A}$ receptor-mediated. Mirtazapine has been said to be a functional "*indirect agonist*" of the 5-HT$_{1A}$ receptor [53]. Mirtazapine's K_i for α_2-adrenergic receptors is ≈ 20 nM, while aripiprazole's K_i for α_2 receptors [α_{2A} K_i 74 nM; α_{2B} K_i 100 nM; α_{2C} 37 nM] [30].

$K_i(^{ARI}/_{BREX})$ for the α_2-adrenergic receptors is, therefore, $\alpha_{2A} \approx 5$; for $\alpha_{2B} \approx 6$ while for $\alpha_{2C} \approx 63$. While we postulated divergent or significantly different effects when the ratio is either $> 10^2$ or $<$ than 10^{-2} a $K_i(^{ARI}/_{BREX}) \approx 63$ at α_{2C} indicates possibly higher efficacy for brexpiprazole. Oosterhof *et al.*, 2014, 2015 argue that brexpiprazole is a full 5-HT$_{1A}$receptor agonist, possibly due to a combined α_{2C} antagonist-HT$_{1A}$ agonist effect [24, 25]. Such an effect combination would be quite similar to that seen with the azapirone derivative tandospirone, where tandospirone is an HT$_{1A}$ partial agonist while its primary metabolite (1-

[4] Kantrowitz M. Chemo Hiccups: Causes of and cures for chemo hiccups. 2009. Available at: http://www.kantrowitz.com/cancerpoints/hiccups.html.

[5] Theriot J, Wermuth HR, Ashurst JV. Antiemetic Serotonin-5-HT3 Receptor Blockers. StatPearls. Treasure Island (FL) 2020.

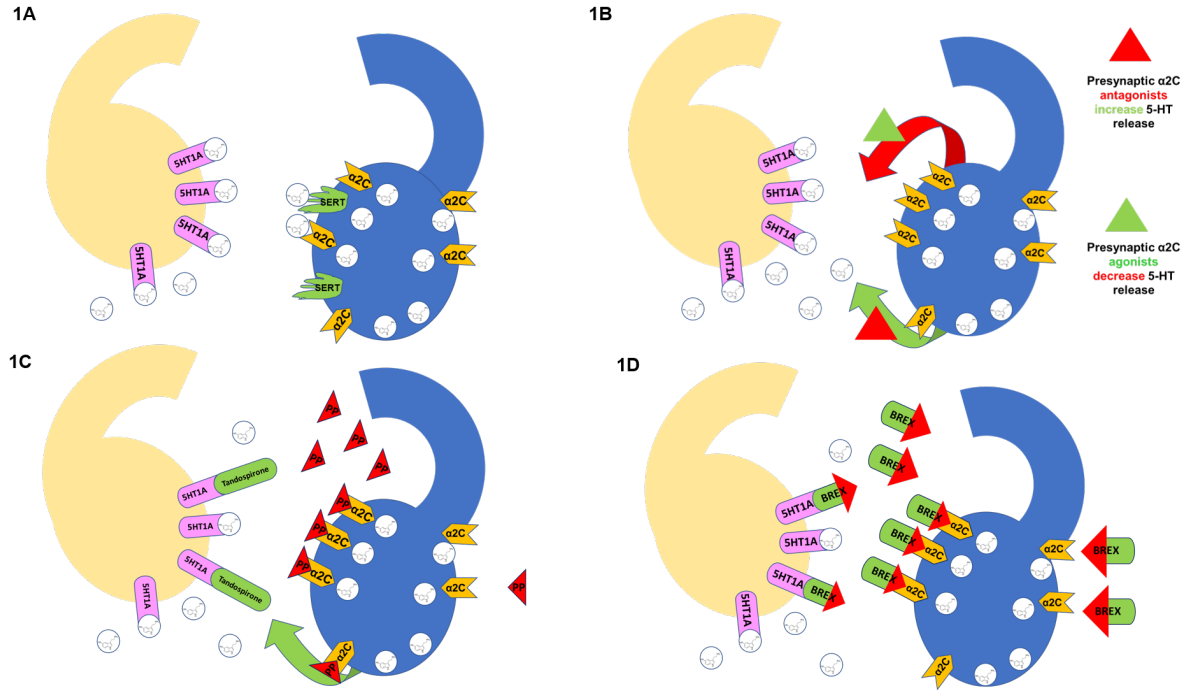

Fig. 1. A schematic illustration showing receptor-drug interaction. 1A. Blue Neuron: α_{2C} adrenergic heteroreceptors control neurotransmitter release (i.e., 5-HT). Once released, 5-HT docks at postsynaptic receptors such as 5-HT$_{1a}$ on the yellow neuron. Activation of presynaptic α_{2C} by the neurotransmitter reduces further release while SERT removes 5-HT from the synaptic cleft. 1B. Activation of presynaptic α_{2C} by the neurotransmitter or drug with agonist effect (green triangle) reduces further release (red arrow). In contrast, the drug with antagonist effect (red triangle) increases neurotransmitter release (green arrow). 1C. The primary metabolite of tandospirone (1-PP) is a highly affine α_{2C} adrenergic antagonist, increasing serotonin release and augmenting postsynaptic effects. Tandospirone is a 5-HT$_{1A}$ partial agonist; the combined effect of drug and metabolite is direct and indirect agonism at 5-HT$_{1A}$ (mirtazapine-like effect). 1D. Brexpiprazole is a highly affine α_{2C} adrenergic antagonist, thus increasing serotonin release and augmenting postsynaptic effects. At the same time, brexpiprazole is also a 5-HT$_{1A}$ partial agonist; the combined effect at the two receptors is direct and indirect agonism at 5-HT$_{1A}$ (mirtazapine-like effect).

pyrimidinyl-piperazine; 1-PP) is a centrally acting, the high-affinity α_2-adrenergic antagonist ($K_i \approx$ 10-40 nM) [54, 55]. Interestingly, tandospirone was successfully used to treat hiccup [56] (See also Fig. 1).

For an overview of α_{2C} receptors, see the recent review from Brian Harvey's group [57].

Activation of 5-HT$_{1A}$ receptors enhances vagal activity; therefore, 5-HT$_{1A}$ agonists (brexpiprazole) would be unlikely to favor hiccup development. In contrast, 5-HT$_{1A}$ partial agonists (week antagonists) such as aripiprazole might not offer the same benefit [50].

5. Conclusions

It is unlikely that a unique receptor-drug interaction could explain the different effects of the examined drugs on hiccup. The different effect is most likely the consequence of several smaller effects at more than one receptor. Brexpiprazole is a highly affine (potent) α_{2C} antagonist and, therefore, also an indirect 5-HT$_{1A}$ agonist. In contrast, aripiprazole is a partial 5-HT$_{1A}$ agonist (weak antagonist) and an HT$_3$ antagonist. Activation of 5-HT$_{1A}$ receptors enhances vagal activity while HT$_3$ blockade reduces it. Vagus nerve activation is therapeutic for hiccups. A definitive answer continues to be elusive.

Abbreviations

5-HT, 5-hydroxytryptamine, serotonin; CNS, Central nervous system; DA, Dopamine; DAT, Dopamine transporter; EC$_{50}$, concentration of a drug that gives a half-maximal response (nM); E$_{max}$, concentration of a drug that gives a maximal response (nM); IC$_{50}$, half maximal inhibitory concentration (nM); K_i, Inhibitor constant (nM); SERT, Serotonin transporter.

Author contributions

Georg Petroianu: planning and conducting the review, literature search, interpreting the literature, and drafting the manuscript; Eman Alefishat: planning and conducting the review, literature search, interpreting the literature, and drafting the manuscript; Lujain Aloum: literature search, interpreting the literature, and drafting the manuscript; Ovidiu Baltatu: literature search, interpreting the literature, and drafting the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

Consent for publication

All authors have read and approved the manuscript for publication.

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