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A possible role for ghrelinergic stimulation through blockade of 5-HT_{2B}/5-HT_{2C} receptors in antiemetic action of olanzapine

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Abstract

Olanzapine, a multi-acting receptor targeted antipsychotic drug, is effective for the prophylaxis as well as the rescue of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy. Several clinical practice guidelines for antiemetic medication have recommended using olanzapine as the standard antiemetic therapy. However, little is known about cellular mechanisms underlying antiemetic action of olanzapine. Possible roles for ghrelin release and ghrelin receptor sensitization through blockade of 5-HT receptor subclasses in the antiemetic action of olanzapine are discussed.

Chemotherapy-induced nausea and vomiting (CINV) was one of most distressing adverse events that patients complain during cancer chemotherapy [1]. However, the management of CINV has been greatly improved since the development of 5-HT_3 receptor antagonists and neurokinin NK_1 receptor antagonists [2-4]. Although the chemotherapy-induced vomiting is almost preventable by the use of the combination of three drugs, including 5-HT_3 receptor antagonist, NK_1 receptor antagonist and dexamethasone, the control of nausea during acute (day 1 of chemotherapy) and delayed periods (days 2-5) of chemotherapy remains unresolved [5,6].

Tan *et al.* [7] reported in a randomized controlled trial (RCT) evaluating the additional effect of olanzapine to the two-drug antiemetic medication consisting of azasetron and dexamethasone in patients receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) that the addition of olanzapine significantly improves the rates of no nausea (69.6% *versus* 30.4%, P<0.05) and no vomiting (78.6% *versus* 56.5%, P<0.05) during delayed period for HEC, and the rates of no nausea (83.1% *versus* 58.1%, P<0.05) and no vomiting (89.2% *versus* 75.8%, P<0.05) during delayed period for MEC. Navari *et al.* [8] also reported in a RCT comparing the effects of olanzapine and aprepitant for prevention of CINV in patients receiving cisplatin ≥70 mg/m^2 or cyclophosphamide ≥500 mg/m^2 and doxorubicin ≥50 mg/m^2 that the rate of no nausea during delayed period is significantly higher in olanzapine group than in aprepitant group (69% *versus* 38%, P<0.01), although the rate of complete response (no emesis, no rescue) is similar between the two groups (77% *versus* 73%). The risk of nausea is particularly high in patients receiving anthracycline/cyclophosphamide combination (AC) chemotherapy for breast cancer. Iihara et al. [9] reported in 779 patients receiving first cycle of chemotherapy of any type of emetogenic risk that AC chemotherapy for breast cancer is at high risk for nausea (odds ratio: 4.955, 95% confidence interval: 1.863–13.18, P=0.001, as determined by a multivariate logistic regression analysis). Nawa-Nishigaki et al [10] showed that the addition of olanzapine (5mg orally per day for 5 days) to the three-drug antiemetic medication containing aprepitant, 5-HT_3 receptor antagonist and dexamethasone remarkably improves the control of nausea, in which the rate of no nausea during delayed period is 89.5% and 50.7% in patients with and without additional olanzapine, respectively (P=0.005). Therefore, it is suggested that olanzapine is highly effective for the prophylaxis of chemotherapy-induced nausea.

Moreover, olanzapine is effective for the remedy of refractory or breakthrough CINV [11-13]. Navari *et al.* [11] showed in a double-blind, randomized phase III trial comparing the effects of olanzapine and metoclopramide on the breakthrough CINV in patients receiving HEC that olanzapine reduces the breakthrough CINV more potently than metoclopramide (68% *versus* 23%, P<0.01, for no nausea, 70% *versus* 31%, P<0.01, for no vomiting). The antiemetic effect of olanzapine has been confirmed by a number of studies [14-16] and their meta-analyses [17-21].

In 2014, the National Comprehensive Cancer Network (NCCN) recommended three-drug antiemetic medication containing olanzapine, palonosetron and dexamethasone as the standard antiemetic regimen for HEC and MEC. Thereafter, four-drug antiemetic medication consisting of olanzapine, 5-HT_3 receptor antagonist, NK_1 receptor antagonist, and dexamethasone is included in the NCCN guideline 2017 and the American Society of Clinical Oncology (ASCO) guideline 2017.

However, it is still uncertain how olanzapine fulfills its antiemetic action. Olanzapine is classified as the multi-acting receptor targeted

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Table 1. Comparison of pKi for various neurotransmitter receptors among atypical and typical antipychotic drugs. Ratio of Ki for dopamine D_2 receptor to Ki for each receptor as represented. pKi values were quoted from Shahid, *et al.* [22]

Receptor	5-HT_{1A}		5-HT_{2A}		5-HT_{2B}		5-HT_{2C}		5-HT_6		5-HT_7		α_{1A}		α_{2C}		H_1		M_1		M_3		D_2
	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	pKi	ratio	
Olanzapine	5.82	0.014	8.88	16.218	8.41	5.495	8.41	5.495	8.49	6.607	7.43	0.575	7.65	0.955	7.39	0.525	8.47	6.310	7.92	1.778	7.47	0.631	7.67
Aripiprazole	8.57	0.427	8.02	0.120	9.59	4.467	7.55	0.041	6.64	0.005	7.46	0.033	6.49	0.004	7.93	0.098	7.69	0.056	5.41	0.0003	5.11	0.0001	8.94
Quetiapine	6.78	2.512	6.81	2.692	7.33	8.913	5.98	0.398	5.64	0.182	7.25	7.413	7.19	6.457	7.42	10.965	7.96	38.019	6.55	1.479	6.29	0.813	6.38
Risperidole	6.75	0.035	9.69	30.200	7.99	0.603	8.17	0.912	5.66	0.003	9.13	8.318	8.29	1.202	8.74	3.388	7.09	0.076	4.57	0.000	4.60	0.0002	8.21
Clozapine	7.06	1.549	8.39	33.113	8.79	83.176	8.56	48.978	8.05	15.136	8.19	20.893	7.90	10.715	8.80	85.114	8.76	77.625	8.29	26.303	7.61	5.495	6.87
Haloperidol	6.29	0.003	7.28	0.028	6.48	0.004	5.79	0.001	5.44	0.0004	7.05	0.016	7.60	0.058	6.88	0.011	5.68	0.001	5.25	0.0003	4.87	0.0001	8.84

(MARTA) antipsychotic drug that shows high affinity for dopamine D_1, D_2, D_3 and D_4 receptors, serotonin 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors, histamine H_1 receptor, muscarinic M_1, M_2, M_3 and M_4 receptors, and adrenergic α_{1A} and α_{2C} receptors [22]. The pKi values of olanzapine for various transmitter receptors are shown in (Table 1). Olanzapine shows higher affinity for 5-HT_{2B} and 5-HT_{2C} receptors (pKi=8.41) than for dopamine D_2 receptor (pKi=7.67). The ratios of Ki value for D_2 receptors to those for 5-HT_{2B} and 5-HT_{2C} receptors are both 5.495, indicating that olanzapine has 5.495-fold higher affinity for 5-HT_{2B} and 5-HT_{2C} receptors than for D_2 receptor. In contrast, the typical antipsychotic drug haloperidol shows negligible affinity for 5-HT_{2B} or 5-HT_{2C} receptor. Moreover, Bymaster *et al.* [23] reported that olanzapine potently inhibits the serotonin-stimulated accumulation of inositol 1,4,5-trisphosphate (IP3) in cell lines transfected with 5-HT_{2A} or 5-HT_{2B} receptors but weakly blocks serotonin-induced IP3 formation in cell lines transfected with 5-HT_{2C} receptors. Taken together, physiologically relevant blockade of 5-HT_{2B} and 5-HT_{2C} receptors occurs after administration of olanzapine. Lord *et al.* [24] reported in mice that the hyperphagia induced by olanzapine is blocked by lorcaserin, a selective 5-HT_{2C} receptor agonist [25], or diminished in 5-HT_{2C} receptor knockout mice, thereby suggesting that olanzapine induces orexigenic action *via* blockade of 5-HT_{2C} receptor.

On the other hand, it has been demonstrated that cisplatin-induced decrease in appetite is mediated by stimulation of 5-HT_{2B} and 5-HT_{2C} receptors and subsequent reduction in the secretion of acylated ghrelin, an appetite-promoting gut peptide [26-28]. Takeda *et al.* [26] reported that administration of cisplatin (1-8mg/kg. i.p.) to rats decreases the plasma level of acylated ghrelin in a dose-dependent manner. Both the decrease in plasma acylated ghrelin and the reduction in food intake induced by cisplatin are reversed by the 5-HT_{2B} receptor antagonist SB215505 and the 5-HT_{2C} receptor antagonist SB242084. In addition, like cisplatin, *m*-chlorophenyl piperazine, a 5-HT_{2C} receptor agonist, or BW723C86, a 5-HT_{2B} receptor agonist, decreases plasma level of acylated ghrelin. These data suggest that serotonin liberated by cisplatin from enterochromaffin cells in guts stimulates both 5-HT_{2B} and 5-HT_{2C} receptors and subsequently inhibits the release of ghrelin, which causes a reduction in appetite.

These findings, taken together, suggest that olanzapine prevents CINV by stimulating the release of ghrelin *via* blockade of 5-HT_{2B} and 5-HT_{2C} receptors.

On the other hand, the modulation of ghrelin receptor signaling by 5-HT_{2C} receptor has been demonstrated. Schellekens *et al.* [29] reported in human embryonic kidney (HEC) 293 cells transfected with the ghrelin receptor GSH-R1a receptor (growth hormone secretagogue receptor) that the elevation of intracellular Ca^{2+} concentration induced by the stimulation of GSH-R1a receptor with ghrelin or its analog MK0677 is remarkably reduced in cells co-transfected with 5-HT_{2C} receptor. They also showed in mice that ghrelin-stimulated food intake is attenuated by the 5-HT_{2C} receptor agonist lorcaserin but augmented by the 5-HT_{2C} receptor antagonist SB242084. More recently, they showed a mode of modulation of GSH-R1a receptor signaling by 5-HT_{2C} receptor [30]. They showed that the stimulation of 5-HT_{2C} receptor facilitates the heterodimerization of GHS-R1a receptor with 5-HT_{2C} receptor and subsequent internalization, thereby resulting in an attenuation of GHS-R1a stimulation-induced elevation of intracellular Ca^{2+} concentration. Moreover, 5-HT_{2C} receptor antagonist reverses the heterodimerization of GHS-R1a with 5-HT_{2C} receptor, which restores the cellular response to the GHS-R1a agonist ghrelin. Huang *et al.* [31] also showed that atypical antipsychotics such as olanzapine, clozapine and risperidone induce weight gain and obesity by blocking 5-HT_{2C} receptor and subsequent activation of GHSR1a signaling, in which reduction in dimerization of GHSR1a receptor with 5-HT_{2C} receptor is involved.

These findings, taken together, suggest that not only the stimulation of ghrelin release by the antagonism of both 5-HT_{2B} and 5-HT_{2C} receptors but also the ghrelin receptor GHSR1a sensitization *via* blockade of 5-HT_{2C} receptor contribute, at least in part, to the antiemetic action of olanzapine.

On the other hand, extensive care should be taken to avoid diabetic adverse events such as diabetic ketoacidosis, particularly in patients with pre-existing diabetes, since atypical antipsychotic drugs, including olanzapine, clozapine and risperidone, cause diabetic ketoacidosis [32,33]. The incidence of hyperglycemic emergencies, including hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, is rare in non-diabetic patients (1-2 per 1000-person years), however, the rate is markedly elevated in patients with pre-existing diabetes (6-12 per 1000 person years) [34]. There are some differences in the rates of diabetic ketoacidosis associated with antipsychotic drugs: the rate of diabetic ketoacidosis is significantly higher in patients receiving olanzapine (0.107%: 55 cases/51,302 patients) than for risperidone (0.060%: 31 cases/51,330), in which adjusted relative risk is 1.62 (P=0.033) [35].

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