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 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 (5 mg 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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Key words: olanzapine, chemotherapy-induced nausea and vomiting, 5-HT$_{2B}$/5-HT$_{2C}$ receptor, highly emetogenic chemotherapy, moderately emetogenic chemotherapy

Received: December 21, 2018; Accepted: January 03, 2019; Published: January 07, 2019
(MARTA) antipsychotic drug that shows high affinity for dopamine D₃, D₄, D₅, and D₆ receptors, serotonin 5-HT₁A, 5-HT₁B, 5-HT₁C, 5-HT₂, and 5-HT₆ receptors, histamine H₁ receptor, muscarinic M₁, M₂, M₃, and M₄ receptors, and adrenergic α₁ and α₂ receptors [22]. The pKi values of olanzapine for various transmitter receptors are shown in (Table 1). Olanzapine shows higher affinity for 5-HT₁A and 5-HT₁C receptors (pKi=8.41) than for dopamine D₁ receptor (pKi=7.67). The ratios of Ki value for D₁ receptors to those for 5-HT₁A and 5-HT₁C receptors are both 5.49, indicating that olanzapine has 5.49-fold higher affinity for 5-HT₁A and 5-HT₁C receptors than for D₁ receptor. In contrast, the typical antipsychotic drug haloperidol shows negligible affinity for 5-HT₁A or 5-HT₁C 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-HT₁A or 5-HT₁C receptors but weakly blocks serotonin-induced IP3 formation in cell lines transfected with 5-HT₂ receptors. Taken together, physiologically relevant blockade of 5-HT₁A and 5-HT₁C 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-HT₂C receptor agonist [25], or diminished in 5-HT₂C receptor knockout mice, thereby suggesting that olanzapine induces orexigenic action via blockade of 5-HT₂C receptor.

On the other hand, it has been demonstrated that cisplatin-induced decrease in appetite is mediated by stimulation of 5-HT₁A and 5-HT₁C 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-HT₁A receptor antagonist SB215505 and the 5-HT₁C receptor antagonist SB242084. In addition, like cisplatin, m-chlorophenylpiperazine, a 5-HT₃₅₆ receptor agonist, or BW23C86, a 5-HT₈ receptor agonist, decreases plasma level of acylated ghrelin. These data suggest that serotonin liberated by cisplatin from enterochromaffin cells in guts stimulates both 5-HT₁A and 5-HT₁C 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-HT₁A and 5-HT₁C receptors. On the other hand, the modulation of ghrelin receptor signaling by 5-HT₁C receptor has been demonstrated. Schellekens et al. [29] reported in human embryonic kidney (HEK) 293 cells transfected with the ghrelin receptor GHS-R1a receptor (growth hormone secretagogue receptor) that the elevation of intracellular Ca²⁺ concentration induced by the stimulation of GHS-R1a receptor with ghrelin or its analog MK0677 is remarkably reduced in cells co-transfected with 5-HT₁C receptor. They also showed in mice that ghrelin-stimulated food intake is attenuated by the 5-HT₁C receptor agonist lorcaserin but augmented by the 5-HT₁C receptor antagonist SB242084. More recently, they showed a mode of modulation of GHS-R1a receptor signaling by 5-HT₁C receptor [30]. They showed that the stimulation of 5-HT₁C receptor facilitates the heterodimerization of GHS-R1a receptor with 5-HT₂C receptor and subsequent internalization, thereby resulting in an attenuation of GHS-R1a stimulation-induced elevation of intracellular Ca²⁺ concentration. Moreover, 5-HT₂C receptor antagonist reverses the heterodimerization of GHS-R1a with 5-HT₂C 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-HT₂C receptor and subsequent activation of GHSR1a signaling, in which reduction in dimerization of GHSR1a receptor with 5-HT₂C receptor is involved.

These findings, taken together, suggest that not only the stimulation of ghrelin release by the antagonism of both 5-HT₁A and 5-HT₁C receptors but also the ghrelin receptor GHSR1a sensitization via blockade of 5-HT₂C 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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**Table 1. Comparison of pKi for various neurotransmitter receptors among atypical and typical antipsychotic drugs.** Ratio of Ki for dopamine D₁ receptor to Ki for each receptor as represented. pKi values were quoted from Shahid, et al. [22].

| Receptor | 5-HT₁A | 5-HT₁B | 5-HT₁C | 5-HT₂ | α₁ | α₂ | H₁ | M₁ | M₄ | D₁ |
|----------|--------|--------|--------|-------|----|----|----|----|----|----|
| pKi      | ratio  | pKi    | ratio  | pKi   | ratio| pKi | ratio| pKi | ratio| pKi |
| Olanzapine | 5.82  | 0.014 | 8.88  | 16.218 | 8.41 | 5.495 | 8.41 | 5.495 | 8.69 | 6.607 |
|  | 7.43  | 0.575 | 7.65  | 0.955 | 7.39 | 0.525 | 8.47 | 6.310 | 7.92 | 1.778 |
| 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 |
| 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 | 0.916 | 7.96 | 3.819 | 6.15 | 1.479 |
| Risperidone | 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 |
| 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 |
| 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 |

**J Transl Sci, 2019 doi: 10.15761/JTS.1000300**

**Volume 5: 2-3**
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