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Validation analysis of Japanese histological classification of breast cancer using the National Summary of Hospital Cancer Registry 2007, Japan

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Using the National Summary of Hospital Cancer Registry 2007, Japan, (HCRJ) from 219 local core cancer hospitals (LCCH) that had registered more than 29 breast cancers, we validated the Japanese classification of breast cancer (JCBC). In JCBC, most invasive ductal carcinomas (IDC) are subclassified as papillotubular carcinoma (coded as 850031 in the HCRJ) or scirrhous carcinoma (850033). Because of the confusing criterion that IDC with substantial ductal carcinoma *in situ* (DCIS) is papillotubular carcinoma, pathological T (pT)1 might be overestimated as pT2–3 by measuring the tumor size to include DCIS at LCCH where papillotubular carcinoma is diagnosed correctly. The LCCH were divided based on the difference between the proportion of papillotubular carcinoma to scirrhous carcinoma (PPS), that is, the proportion of 850031 cases to the sum of 850031 and 850033 cases at each LCCH (mean: 45.6%), and the PPS of the LCCH whose in-house histological classification was the origin of JCBC (standard PPS [StPPS]: 42.3%), into G5 (PPS within StPPS ± 5%), L5 (PPS < StPPS–5%), HL (StPPS + 15% ≥ PPS > StPPS + 5%), and HH (PPS > StPPS + 15%). On pT2–3, the proportion of N1–3 cases to N0 in G5 and HL was significantly lower than that in L5. The averages of the proportion at each LCCH of G5 and HL were also significantly lower than that of L5. Meanwhile, on pT1, the proportions and averages were not significantly different among the groups. The frequent overestimation of pT in G5 and HL explains their lower frequency of lymph nodal metastasis on pT2–3, leaving the frequency on pT1 unchanged. The JCBC has spoiled the accuracy of pTNM. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2011.01984.x, 2011)

The National Summary of Hospital Cancer Registry 2007, Japan (NS/HCRJ), from 356 local core cancer hospitals (LCCH), was the first nationwide accumulation of hospital cancer registry data in Japan.[1] At least one hospital is designated as an LCCH in a secondary medical service area on the basis of the Cancer Control Act of Japan. Although the NS/HCRJ is not an inventory survey, it is a collection of more detailed information on cancers than the regional cancer registry in Japan. Using breast cancer as an example, we show that the NS/HCRJ can work as a tool to elucidate problems in cancer care in Japan.

In Japan, breast cancer is diagnosed according to the General Rules for Clinical and Pathological Recording of Breast Cancer (Japanese classification of breast cancer [JCBC]) provided by the Japanese Breast Cancer Society.[2] Invasive ductal carcinoma (IDC) is the most common histological subtype of breast cancer.[3] In the JCBC, the common type of IDC is divided into three subtypes: papillotubular carcinoma, solid-tubular carcinoma, and scirrhous carcinoma[2] (Table 1). According to the JCBC definition, scirrhous carcinoma is the least differentiated, solid-tubular carcinoma is moderately differentiated, and papillotubular carcinoma is the best differentiated of the three. In the Japanese hospital cancer registry, papillotubular carcinoma, solid-tubular carcinoma, and scirrhous carcinoma are coded as 850031, 850032, and 850033, respectively, although they are not included in the ICD-O-3. This rule was repeatedly announced in the seminars for tumor registrars held by the National Cancer Center of Japan, and was included in the textbook for Japanese tumor registrars.

Pathologists and oncologists outside of Japan will not be familiar with this classification. In addition, Japanese pathologists and oncologists are also not sufficiently well informed regarding this matter, although most of them routinely use the terminology. The histology of papillotubular carcinoma is different from what the English name "papillotubular" implies.[2] Papillotubular carcinoma includes heterogeneous groups, such as IDC with substantial ductal carcinoma *in situ* (DCIS); papillary carcinoma with an invasive component; and IDC with a tubular structure, but without a massive solid component or fibrous stroma. The concept that an IDC is classified based on the presence of DCIS is confusing. Some pathologists diagnose an IDC with DCIS as papillotubular carcinoma, as prescribed by the JCBC, while others diagnose it as "scirrhous carcinoma with DCIS", although this description is not correct in JCBC, or just as "IDC with DCIS", as in the World Health Organization classification, without using the JCBC.

More than half of Japanese pathologists are not aware of the rule that a non-invasive component is not to be included in the tumor size when pathological T (pT) is determined.[4,5] The pT1–3 of breast cancer is defined by tumor size.[6,7] At an LCCH where pathologists diagnose papillotubular carcinoma correctly according to the definition of the JCBC, there might be a larger risk that the pathologists, clinicians, and tumor registrars will overestimate a tumor size by measuring papillotubular carcinoma comprised of IDC and DCIS than at a LCCH where pathologists use the terminology "scirrhous carcinoma with DCIS" or "IDC with DCIS". Since both scirrhous carcinoma and IDC G3, were coded as 850033, the latter LCCH have more 850033 breast cancer cases and fewer 850031 breast cancer cases than the former. The relationship between pT and papillotubular carcinoma is summarized in Figures 1 and 2.

Materials and Methods

The NS/HCRJ was provided from the Hospital Cancer Registry Section, National Cancer Center (Tokyo, Japan). C50.0-C50.9 cases were extracted from the NS/HCRJ. The proportion of 850031 cases to the sum of 850031 and 850033 cases was calculated as the indicator for the proportion of cases diagnosed as papillotubular carcinoma to scirrhous carcinoma (PPS) (Table 2). The PPS at each LCCH was 45.6% on average; 21.2% in SD. The PPS of the LCCH that treats the greatest number of breast cancers in Japan was used as the standard

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Table 1. Invasive ductal carcinoma (IDC) of the common type in the Japanese classification of breast cancer (JCBC)

JCBC	ICD-0 code in the HCRJ	Tumor grade in the JCBC	In the WHO classification
Papillotubular carcinoma	850031	G1	IDC, IDC + DCIS, or papillary carcinoma etc.
Solid-tubular carcinoma	850032	G2	IDC
Scirrhous carcinoma	850033	G3	IDC

DCIS, ductal carcinoma *in situ*; HCRJ, Hospital Cancer Registry in Japan.

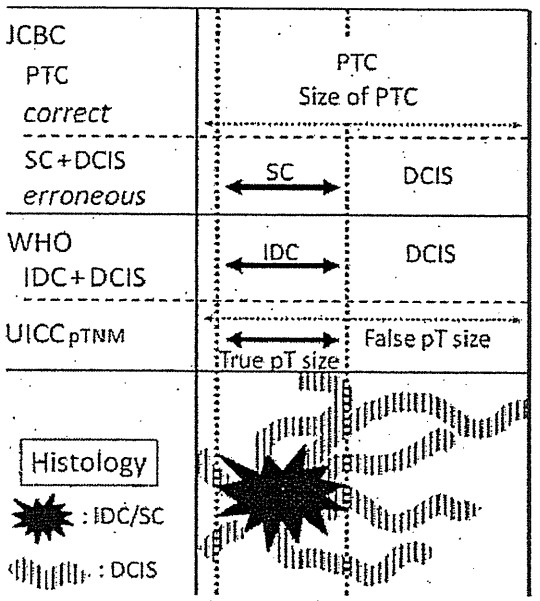

Fig. 1. Relationship between pathological T (pT) and histological classification of breast cancer. Breast cancer consisting of invasive ductal carcinoma (IDC) and ductal carcinoma *in situ* (DCIS) in the World Health Organization (WHO) classification system is a papillotubular carcinoma (PTC) in the Japanese classification of breast cancer (JCBC). Tumor size of a PTC is a mixture of IDC and DCIS, but this is a false pT size (dashed arrow). True Union Internationale Contra le Cancer (UICC) pT size is the measurement of an invasive component (solid arrow). Some Japanese pathologists diagnose PTC as scirrhous carcinoma (SC) with DCIS, although it is incorrect in the JCBC, or as IDC with DCIS as in the WHO classification. The size of SC or IDC is the true pT size. Solid polygon indicates SC/IDC, and the dashed lines indicate DCIS.

(StPPS = 42.3%), since the JCBC was based on its in-house histological classification. Each LCCH was divided into three groups, according to its PPS: H5 (higher PPS than StPPS + 5%), G5 (good PPS within StPPS ± 5%), and L5 (lower PPS than StPPS–5%) (Table 3). In L5, papillotubular carcinoma was supposed to be diagnosed as scirrhous carcinoma or IDC, grade 3, with DCIS more frequently than in G5 and H5. In G5, papillotubular carcinoma was diagnosed in good proportion, compared to the StPPS. H5 was further divided into HL (StPPS + 15% ≥ PPS > StPPS + 5%) and HH (PPS > StPPS + 15%) for a subanalysis.

In the NS/HCRJ, TNM was classified according to the Union Internationale Contra le Cancer (UICC) TNM sixth edition.[7] The proportion of lymph node metastasis-positive cases to negative ones among pT2–3 breast cancers and that among pT1 breast cancers were calculated for each group and for each LCCH (Table 2). The proportion of pTisN0 to pT1–4N0 cases was also calculated for each group and for each LCCH. A higher proportion of pTisN0 to pT1–4N0 indicated that invasion was more readily identified by the pathologists in that group. The 137 LCCH that registered <30 breast cancer cases with pTNM were excluded from the study.

The proportions for each group were compared by the chi square-test using StatMateIII (ATMS, Tokyo, Japan). The averages of the proportion at each LCCH of the groups were compared using one-sided Welch's *t*-test.[8] Significance was accepted when the *P*-value was <0.05.

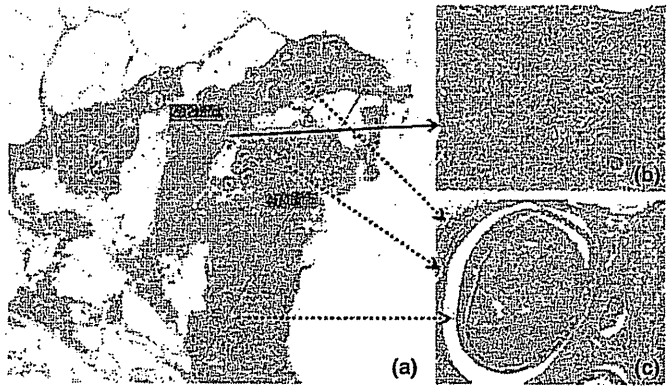

Fig. 2. Papillotubular carcinoma consisting of invasive ductal carcinoma (IDC) and ductal carcinoma *in situ* (DCIS). (a) IDC with DCIS corresponds to a papillotubular carcinoma in the Japanese classification of breast cancer (JCBC). Size of the papillotubular carcinoma was 2.1 cm (false pathological T [pT]), and that of IDC was 0.2 cm (true pT size). Tumor was not pT2, but pT1. Original magnification ×1. (b) Some pathologists erroneously diagnose the invasive component of the carcinoma as "scirrhous carcinoma" in the JCBC. Original magnification ×40. (c) DCIS is an inseparable component of papillotubular carcinoma. Original magnification ×40.

Results

Breast cancers registered as 85003. The number of breast cancer cases registered in the NS/HCRJ was 31 233. pTNM was registered in 22 121 of the cases, of which 16 366 cases were recorded as 85003X, and subdivided as follows: 850031, 5223 cases; 850032, 3264 cases; 850033, 6180 cases; and 850034–850039, 1699 cases. In this study, the 85003 cases with pTNM were analyzed (Table 4). The proportions of 850031, 850032, and 850033 cases were approximately 32%, 20%, and 38%, respectively (roughly 3:2:4), which was comparable to the proportion of papillotubular carcinoma, solid-tubular carcinoma, and scirrhous carcinoma in the annual report of the JCBC[9] of 26%, 16%, and 32% of all breast cancers, respectively (roughly 3:2:4). In an original report of the Nottingham histological grade, the proportion of grades 1–3 of invasive breast cancers were roughly 4:7:10.[10] This result indicates that the coding system of the Japanese hospital cancer registry for papillotubular carcinoma, solid-tubular carcinoma, and scirrhous carcinoma was working in most LCCH. The total numbers of pTis, pT1, pT2, pT3, and pT4 were 2550, 11 610, 6517, 750, and 694, respectively. Excluding LCCH that registered fewer than 30 breast cancer cases with pTNM, the total numbers of pTis, pT1, pT2, pT3, and pT4 were 2450, 10 925, 6063, 695, and 620, respectively.

Comparison of the frequency of lymph node metastasis of breast cancers. The proportion of lymph node metastasis-positive cases to negative ones on pT2–3 breast cancers was

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Table 2. Abbreviations used in this report

Abbreviations	Definition	Remarks
LCCH	Local core cancer hospital	At least one hospital was designated as LCCH in a secondary medical service area in Japan
JCBC	Japanese Classification of Breast Cancer	Based on the General Rules for Clinical and Pathological Recording of Breast Cancer
PPS	(No. of 850031 cases) ÷ (sum of 850031 cases and 850033 cases)	The proportion of papillotubular carcinoma to scirrhous carcinoma cases. Mean, 45.6%; SD, 21.2%
StPPS	PPS of the LCCH whose in-house histology classification was the origin of the JCBC	Standard PPS, 42.3%. This LCCH treats the most breast cancers in Japan

Table 3. Grouping of local core cancer hospitals (LCCH) by the proportion of papillotubular carcinoma to scirrhous carcinoma cases (PPS)

Groups	Description	No. LCCHs
L5	PPS < StPPS–5%	76
G5	StPPS + 5% ≥ PPS ≥ StPPS ± 5%	50
H5	PPS > StPPS + 5%	93
HL	StPPS + 15% ≥ PPS > StPPS + 5%	38
HH	PPS > StPPS + 15%	55

It was supposed that papillotubular carcinoma was diagnosed more frequently in H5, less frequently in L5, and at the proper frequency in G5. H5 was also divided into HL and HH for subanalysis. In L5, many pathologists would diagnose papillotubular carcinoma as scirrhous carcinoma with ductal carcinoma *in situ* (DCIS) or just invasive ductal carcinoma, Grade 3 with DCIS. StPPS, standard PPS.

Table 4. Number of cases coded as 85003 in the National Summary of Hospital Cancer Registry 2007, Japan

Code	No. cases	In pTNM cases (%)†	In 85003 cases (%)‡
850031	5223	23.6	31.9
850032	3264	14.8	19.9
850033	6180	27.9	37.8
Total	14 667	66.3	89.6

†Proportion of 850031-3 to operated cases; ‡proportion of the 850031-3 cases to 85003 cases (16 366).

Table 5. Lymph node metastasis of pathological T (pT)2–3 breast cancers in the groups divided by papillotubular carcinoma to scirrhous carcinoma cases

Group	No. cases		N1–3/N0	P (χ^2-test) *vs* L5
	pT2–3–N1–3	pT2–3–N0		
L5	1060	1309	0.810	–
G5	629	893	0.704	0.036 (S)
H5	1203	1623	0.741	0.130 (NS)
HL	499	709	0.704	0.049 (S)
HH	707	914	0.774	0.500 (NS)

N1–3/N0, (pT2–3–N1–3 cases) ÷ (pT2–3–N0 cases). H5 *vs* G5 ($P = 0.41$). HH *vs* G5 ($P = 0.19$). HL *vs* HH ($P = 0.23$). NS, not significant ($P \geq 0.05$); S, significant ($P < 0.05$). χ^2-test.

Table 6. Average of the lymph node metastasis frequency of pathological T (pT)2–3 breast cancers at each local core cancer hospital (LCCH) in the groups divided by papillotubular carcinoma to scirrhous carcinoma cases

Group	Average of N1–3 cases to N0 at each LCCH	P (Welch's t-test) *vs* L5
L5	0.927	–
G5	0.768	0.045 (S)
H5	0.804	0.060 (NS)
HL	0.756	0.029 (S)
HH	0.837	0.15 (NS)

N1–3/N0, (pT2–3–N1–3 cases) ÷ (pT2–3–N0 cases). H5 *vs* G5 ($P = 0.31$, NS). HH *vs* G5 ($P = 0.078$). HL *vs* HH ($P = 0.24$). NS, not significant ($P \geq 0.05$); S, significant ($P < 0.05$). One-sided Welch's t-test.

significantly lower in G5 than in L5 ($P = 0.036 < 0.05$, χ^2-test) (Table 5). The average of the proportion of lymph node metastasis-positive cases to negative ones on pT2–3 breast cancers at each LCCH of G5 was also lower than that of L5 ($P = 0.045 < 0.05$, one-sided Welch's t-test) (Table 6). This result indicated that the lymph node metastasis of pT2–3 breast cancer cases was significantly less frequent in G5, based on either a comparison of the total number of cases or a comparison of the average frequency at each LCCH.

The proportion of lymph node metastasis-positive cases to negative ones on pT2–3 breast cancers of H5, and the average of the proportion at each LCCH of H5, were considerably lower than those of L5, but without significance ($P = 0.13$. χ^2-test and $P = 0.06$, one-sided Welch's t-test, respectively). However, the proportion of lymph node metastasis-positive cases to negative ones on pT2–3 breast cancers, and the average of the proportions at each LCCH of HL, were significantly lower than those of L5 ($P = 0.049 < 0.05$. χ^2-test and $P = 0.029 < 0.05$, one-sided Welch's t-test, respectively). The proportions were almost equal to those of G5 (Tables 5 and 6). Meanwhile, those of HH and L5 were not significantly different ($P = 0.50$. χ^2-test and $P = 0.15$, one-sided Welch's t-test, respectively).

The frequency of lymph node metastasis of pT1 breast cancer cases was not significantly different between the three groups (H5, G5, and L5), either by a comparison of the total number of cases (chi square -test) or a comparison of the average frequency at each LCCH (one-sided Welch's t-test) (Tables 7 and 8).

Proportion of non-invasive carcinoma to invasive carcinoma in pN0 breast cancers. G5 had a significantly lower proportion of pTispN0 cases to pT1–4pN0 ones ($P = 0.004 < 001$, χ^2-test; Table 9), and a significantly lower average of pTispN0 to pT1–4pN0 at each LCCH than that of L5 ($P = 0.049 < 0.05$, Welch's t-test; Table 10). This result was also true for H5 versus L5 ($P = 0.0013 < 001$, χ^2-test; Table 9. $P = 0.037 < 0.05$, Welch's t-test; Table 10). For some reason, pTis was less frequent in G5 and H5 than in L5, both by comparison of the total number of

Table 7. Lymph node metastasis of pathological T (pT)1 breast cancers in the groups divided by papillotubular carcinoma to scirrhous carcinoma cases

Group	No. cases		N1–3/N0	P (χ^2-test)
	pT1–N1–3	pT1–N0		
L5	730	2940	0.248	NS in each combination
G5	538	2203	0.244	
H5	875	3603	0.243	

N1–3/N0, (pT1–N1–3 cases) ÷ (pT1–N0 cases). L5 *vs* G5 ($P = 0.79$), L5 *vs* H5 ($P = 0.69$), H5 *vs* G5 ($P = 0.93$). NS, not significant. χ^2-test.

Table 8. Average of the lymph node metastasis frequency of pathological T (pT)1 breast cancers at each local core cancer hospital (LCCHs) in the groups divided by papillotubular carcinoma to scirrhous carcinoma cases

Group	Average of N1–3/N0 at each LCCH	P (Welch's t-test)
L5	0.238	NS in each combination
G5	0.250	
H5	0.252	

N1–3/N0: (pT1–N1–3 cases) ÷ (pT1–N0 cases). L5 *vs* G5 ($P = 0.31$), L5 *vs* H5 ($P = 0.47$), H5 *vs* G5 ($P = 0.25$, not significant [NS]). One-sided Welch's t-test.

Table 9. Proportion of noninvasive carcinomas to invasive carcinomas in pN0 breast cancers at each group divided by papillotubular carcinoma to scirrhous carcinoma cases

Group	No. cases		pTis/pT1–4	P (χ^2-test) *vs* L5
	pTisN0	pT1–4N0		
L5	938	6273	0.150	–
G5	539	4416	0.122	0.004 (S)
H5	973	7614	0.128	0.0013 (S)

pTis/pT1–4: (pTisN0 cases) ÷ (pT1–4N0 cases). H5 *vs* G5 ($P = 0.96$, not significant). pT, pathological T; S, significant ($P < 0.05$). χ^2-test.

Table 10. Average of the proportion of non-invasive carcinomas to invasive carcinomas in pN0 breast cancers at each local core cancer hospital (LCCH) in the groups divided by papillotubular carcinoma to scirrhous carcinoma cases

Group (n)	Average of pTis/pT1–4 at each LCCH	P (Welch's t-test) *vs* L5
L5	0.1289	–
G5	0.1034	0.049 (S)
H5	0.1103	0.037 (S)

pTis/pT1–4, (pTisN0 cases) ÷ (pT1–4N0 cases). H5 *vs* G5 ($P = 0.101$, not significant). pT, pathological T; S, significant ($P < 0.05$). One-sided Welch's t-test.

cases and by comparison of the average frequency at each LCCH.

Discussion

In the present study, we have shown that the frequency of lymph node metastasis of pT2–3 breast cancer cases of G5 was significantly lower than that of L5, while that of pT1 breast cancer was not significantly different between the groups. We believe this was due to the overestimation of pT of papillotubular carcinoma. The tumor size of the carcinoma includes a mixture of IDC and DCIS. However, the pT of papillotubular carcinoma must be decided based on the size of an invasive component. Pathological T2–3 breast cancer in G5 must have contained a proportion of false pT2–3 cases, which should have been diagnosed as pT1. Meanwhile, the frequency of lymph node metastasis of pT1 breast cancer was similar among the groups. Even if proportional cases of false pT2–3 cases/true pT1 cases shifted to pT2–3, the rest of the pT1 cases were true pT1. It is quite unlikely that pTNM was diagnosed in the same manner between G5 and L5, and that breast cancers at G5 LCCH actually had lower metastatic ability than those at L5 LCCH.

Although H5 had a considerably lower proportion of lymph node metastasis on pT2–3 breast cancers than L5, the difference was not significant (Tables 5 and 6). In the subanalysis, H5 was divided into HL (StPPS + 15% = 57.3% ≥ PPS > StPPS + 5% = 47.3%, a high PPS group) and HH (PPS > 57.3%, an extremely-high PPS group). At PPS = 57.3%, the proportion of papillotubular carcinoma to scirrhous carcinoma was approximately 4:3, if all the cases were diagnosed according to the JCBC, while the proper proportion was approximately 3:4. Therefore, it was unlikely that breast cancers were diagnosed according to the JCBC and recorded according to the Japanese cancer registry rule at most LCCH in HH (an extremely-high PPS group). The proportion of cases diagnosed as papillotubular carcinoma to scirrhous carcinoma can be high at LCCH where a code 850033 is not used or infrequently used. In such LCCH, IDC might be diagnosed without tumor grade (coded as 850039), scirrhous carcinoma might be coded as 814033 (a code for "scirrhous carcinoma of the stomach" in Japan) or 814133 (a common code for a scirrhous carcinoma in ICD-O), or some data format error might have occurred.

In HL (H5 without HH), the frequency of lymph node metastasis on pT2–3 breast cancers was almost equal to that in G5 and significantly lower than that in L5. This revealed that both G5 (the proper PPS group) and HL (the high PPS group) have a common denominator.

We also showed that pTis was less frequent in G5 and H5. One might suspect that pTis was less prevalent in the LCCH of G5 and H5, but this is unlikely. A more likely explanation is that the pathologists of G5 and H5 more readily regarded a lesion as invasive than those of L5. Pathologists who prefer a diagnosis of papillotubular carcinoma might care less about the difference in DCIS and IDC.

It is almost self-evident from the definition of papillotubular carcinoma in the JCBC that there is a major risk for overestimation of pT, when including both IDC and DCIS in determining the pT size. In this study, we used the NS/HCRJ to show, for the first time, that this suspicion is true. The present study provides the only statistical analysis of the data from many LCCH. We do not claim that pT is always overestimated in all of the G5 LCCH. In fact, we believe that pT is properly evaluated in a substantial proportion of G5 LCCH. However, the purpose of the TNM can be undermined easily by contamination of incorrectly-assigned TNM, unless we protect its accuracy.[4,11–13]

We believe that the JCBC spoils the accuracy of the pTNM system and the reliability of the research in this field taking place in Japan. To improve the accuracy of the pTNM, it would be advisable to modify the JCBC in the near future, or just to use the World Health Organization classification instead. TNM is an extremely important indicator for the selection of the treatment method in the prediction of a patient's prognosis and for grouping patients for various investigations.[6,7,12]

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Although the JCBC is the local classification of breast cancer in Japan, there might be similar local rules on breast cancer or other cancers in the other countries. Since pTNM is not included in the organ-specific cancer registry of the JCBC, data from outside of the Japanese Breast Cancer Society were necessary for this analysis. Although the NS/HCRJ was used as an organ-specific cancer registry in this study, it proved to be a useful tool to elucidate national problems of breast cancer therapy. A validation analysis using the NS/HCRJ in this way will be applicable to cancers other than breast cancer and for procedures other than pathology diagnoses.

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Disclosure Statement

The authors have no conflict of interest.

Usefulness of Olanzapine as an Adjunct to Opioid Treatment and for the Treatment of Neuropathic Pain

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ABSTRACT

Background: The use of opioids for pain management is often associated with nausea and vomiting. Although conventional antipsychotics are often used to counter emesis, they can be associated with extrapyramidal symptoms. However, chronic pain can induce sleep disturbance. The authors investigated the effects of the atypical antipsychotic olanzapine on morphine-induced emesis and the sleep dysregulation associated with chronic pain.

Methods: A receptor binding assay was performed using mouse whole brain tissue. The emetic response in ferrets was evaluated by counting retching and vomiting behaviors. Catalepsy in mice was evaluated by placing both of their forepaws over a horizontal bar. Released dopamine was measured by an *in vivo* microdialysis study. Sleep disturbance in mice in a neuropathic pain-like state was assayed by electroencephalogram and electromyogram recordings.

Results: Olanzapine showed high affinity for muscarinic M_1 receptor in brain tissue. Olanzapine decreased morphine-induced nausea and vomiting in a dose-dependent manner. However, olanzapine at a dose that had an antiemetic effect (0.03 mg/kg) did not induce catalepsy or hyperglycemia. In addition, olanzapine at this dose had no effect on the morphine-induced release of dopamine or inhibition of gastrointestinal transit. Finally, olanzapine inhibited thermal hyperalgesia and completely alleviated the sleep disturbance induced by sciatic nerve ligation.

Conclusion: These findings suggest that olanzapine may be useful for the treatment of morphine-induced emesis and as an adjunct for the treatment of neuropathic pain associated with sleep disturbance.

What We Already Know about This Topic

- Chronic pain is often associated with sleep disturbances
- Severe side effects of opioids given for pain treatment include nausea and vomiting

What This Article Tells Us That Is New

- In ferrets, olanzapine, an atypical thienobenzodiazepine antipsychotic drug, suppressed morphine-induced emesis and improved pain-related sleep disturbances

THE World Health Organization[1] has stated that morphine is the "gold standard" for the treatment of moderate to severe pain caused by cancer. However, the use of morphine for this purpose is often associated with distressing side effects, such as drowsiness, constipation, emesis, and delirium.[2,3] Many clinicians consider that dopamine receptor antagonists, including prochlorperazine, are the preferred drugs for combating opioid-induced nausea and vomiting.[2,3] However, these drugs often produce adverse effects, including extrapyramidal symptoms.[4] Therefore, new approaches are needed to prevent opioid-induced emesis, as is a better understanding of the mechanism of drug action.

Nausea and vomiting are controlled by the "vomiting center" in the medulla oblongata,[5] which receives signals from the chemoreceptor trigger zone (CTZ) in the area postrema, the gastrointestinal tract, the vestibular apparatus in the temporal lobe, and the cerebral cortex.[6] Opioids have emetogenic effects by stimulating the CTZ and the vestibular apparatus and by inhibiting gut motility.[7] Although stimu-

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lation of the CTZ by opioids involves opioid μ and δ receptors,[8] signals from the CTZ to the vomiting center mainly involve dopamine D_2 and serotonin ($5\text{-}HT_3$) receptors in the former. However, opioid-induced stimulation of the vestibular apparatus and subsequent sensory input to the vomiting center have both been suggested to involve histamine H_1 and muscarinic acetylcholine pathways.[9]

Atypical antipsychotic medications treat the positive symptoms of schizophrenia, such as hallucinations and delusions, more effectively than the negative symptoms, such as lack of motivation and social withdrawal. Olanzapine is a newer atypical antipsychotic that blocks dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors for multiple neurotransmitters. Because it affects neurotransmitters that are associated with nausea, it may have potential as an antiemetic medication.[10]

In addition, patients with chronic pain commonly experience sleep disturbance[11–13] and may benefit from its treatment.[13] Sleep problems and daytime sleepiness seem to be related to depression and the severity of pain.[14] It has been suggested that olanzapine may improve sleep disturbance.[15]

The primary endpoint of the study was to investigate whether olanzapine at doses lower than those that would induce catalepsy could suppress morphine-induced emesis with few side effects. We also examined if olanzapine could improve sleep dysregulation under a neuropathic pain-like state.

Materials and Methods

The present study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals at Hoshi University, as adopted by the Committee on Animal Research of Hoshi University (Tokyo, Japan). Every effort was made to minimize the numbers and suffering of animals used in the following experiments.

The observer was not blinded in all of the experiments.

Animals

In the present study, male Institute of Cancer Research mice (20–25 g) (Tokyo Laboratory Animals Science, Tokyo, Japan), male C57BL/6J mice (25–30 g) (CLEA Japan, Tokyo, Japan), and Sprague-Dawley rats (200–300 g) (Tokyo Laboratory Animals Science) were used. Animals were housed in a room maintained at 22° ± 1°C with a 12-h light–dark cycle. Food and water were available *ad libitum*. Each animal was used only once. Male ferrets weighing 1–1.5 kg were obtained from Marshall Research Labs (North Rose, NY) and housed individually in a room kept at 23° ± 1°C under a 12-h light–dark cycle (lights on 8:00 AM-8:00 PM). They were given a standard cat diet (70–80 g/animal, Oriental Yeast Co. Ltd., Chiba, Japan) and allowed free access to water.

Receptor Binding Assay

Mouse whole brain was treated as described previously,[16] and the resulting pellet was resuspended and used as the membrane fraction. The binding assay was performed in triplicate with [^{3}H]clozapine (specific activity, 70–87 Ci/mmol; American Radiolabeled Chemicals, St. Louis, MO) at 0.2 nM, [^{3}H]ketanserin hydrochloride (specific activity, 67 Ci/mmol; PerkinElmer, Waltham, MA) at 0.5 nM, [^{3}H]BRL-43694 (granisetron) (specific activity, 85.3 Ci/mmol; PerkinElmer) at 0.5 nM, [^{3}H]GR113808 (specific activity, 78.3 Ci/mmol; PerkinElmer) at 0.5 nM, [^{3}H]pyrilamine (specific activity, 30 Ci/mmol; PerkinElmer) at 0.5 nM, and [^{3}H]pirenzepine (specific activity, 72.8 Ci/mmol; PerkinElmer) at 0.5 nM, in a final volume of 500 ml that contained 50 mM Tris-HCl buffer, pH 7.4, and 200 ml homogenized membrane fraction. Ninety to 140 mg membrane proteins were used in each assay. Specific binding was defined as the difference in binding observed in the absence and presence of 1 mM unlabeled clozapine, ketanserin, granisetron, or GR113808, 10 mM unlabeled pyrilamine, or 100 mM unlabeled pirenzepine, respectively. All samples were incubated as described previously,[16] and radioactivity in the samples was determined with a liquid scintillation analyzer. All receptor binding curves were fitted using Prism software (version 5.0a; GraphPad Software, La Jolla, CA).

Evaluation of the Emetic Response

Emesis in ferrets after the administration of morphine (0.6 mg/kg, subcutaneous injection) was evaluated by counting the number of retching or vomiting behaviors as described elsewhere,[17] where retching was defined as a rhythmic abdominal contraction without expulsion and vomiting was the oral expulsion of solid or liquid from the gastrointestinal tract. Emesis was assessed for 30 min after the injection of morphine.[18] To determine the effect of olanzapine on morphine-induced emesis, groups of ferrets were pretreated with olanzapine 30 min before the injection of morphine.

An interval of at least 7 days was allowed between testing for each animal to allow for drug washout and to minimize the development of tolerance.

Horizontal Bar Test for the Evaluation of Catalepsy

Catalepsy[19,20] was evaluated using the horizontal bar test as described previously.[21] Briefly, animals were placed so that both forepaws were over a horizontal bar 5 cm above the floor, and the amount of time (s) the animal maintained this position was recorded for as long as 60 s. Catalepsy was considered to have finished when a forepaw touched the floor or when the mouse climbed on the bar. Scores were assigned based on the duration of the cataleptic posture (score 1: 15 to 29 s, score 2: 30 to 59 s, score 3: 60 s or more).

In vivo *Microdialysis Study and Quantification of Dopamine and Its Metabolites*

After 3 days of habituation to the main animal colony, all of the rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal administration) for surgery as described previously.[21] Briefly, the anesthetized animals were placed in a stereotaxic apparatus, the skull was exposed, and a small hole was made using a dental drill. A guide cannula (AG-8; Eicom, Kyoto, Japan) was implanted into the nucleus accumbens (from the bregma: anterior, +4.0 mm; lateral, −0.8 mm; ventral, −6.8 mm; angle 16 degrees) according to the atlas of Paxinos and Watson[22] and fixed to the skull with cranioplastic cement. Three to 5 days after surgery, microdialysis probes (A-I-8–02; 2 mm membrane length; Eicom) were slowly inserted into the nucleus accumbens through guide cannulas during anesthesia with diethyl ether, and the rats were placed in experimental cages (30 cm wide × 30 cm deep × 30 cm high). The probes were perfused continuously (2 ml/min) with artificial cerebrospinal fluid: 0.9 mM $MgCl_2$, 147.0 mM NaCl, 4.0 mM KCl, and 1.2 mM $CaCl_2$. Outflow fractions were collected every 20 min. After three baseline fractions were collected from the rat nucleus accumbens, rats were given olanzapine (0.3 mg/kg, intraperitoneal administration), vehicle (5% dimethyl sulfoxide [DMSO]); 1 ml/kg, intraperitoneal administration) or saline (1 ml/kg, intraperitoneal administration) 30 min before treatment with morphine (10 mg/kg, intraperitoneal administration). Dialysis samples were collected for 180 min after treatment and analyzed by high-performance liquid chromatography (Eicom) with electrochemical detection (Eicom). Dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenyl acetic acid, were separated by column chromatography and identified and quantified by the use of standards, as described previously.[21]

Gastrointestinal Transit

In the study of gastrointestinal transit,[23] Institute of Cancer Research mice were fasted for 12 h before the experiments. Groups of mice were pretreated with olanzapine (0.03–1 mg/kg, subcutaneous injection) or vehicle (5% DMSO) 30 min before the administration of morphine (0.7 mg/kg, subcutaneous injection) or saline, and ink (0.3 ml/mouse) was orally administered 20 min after the injection of morphine or saline. Twenty minutes after the administration of ink, the animal was killed by cervical dislocation, and the small intestine was removed. The percentage inhibition of gastrointestinal transit was calculated as follows: (distance traveled by the ink/length from the pylorus to the cecum) × 100.

Blood Glucose Measurement

C57BL/6J mice were administered olanzapine (0.03–1 mg/kg, subcutaneous injection) or vehicle (5% DMSO) once a day for 1 week. At 60 min after the final injection, the tail was cut and blood was collected. Blood glucose was measured using a self-monitoring blood glucose meter (Medisafe-Mini; Terumo, Tokyo, Japan). The Medisafe-Mini system is based on the optoelectric colorimetry method.

Neuropathic Pain Model

C57BL/6J mice were anesthetized with 3% isoflurane. A partial sciatic nerve ligation model was made by tying a tight ligature with 8–0 silk suture around approximately one third to one half the diameter of the sciatic nerve on the right side (ipsilateral side) under a light microscope (SD30; Olympus, Tokyo, Japan). In sham-operated mice, the nerve was exposed without ligation.

Measurement of Thermal Thresholds

The sensitivity to thermal stimulation was measured as described previously.[24] Briefly, the right plantar surface of mice was exposed to a well-focused radiant heat light source (model 33 Analgesia Meter; IITC/Life Science Instruments, Woodland Hills, CA) that had been adjusted so that the average baseline latency of paw withdrawal in naive mice was approximately 8–10 s. Only quick movements of the hind paw away from the stimulus were considered to be a withdrawal response: paw movements associated with locomotion or weight shifting were not counted as a response. The paws were measured alternating between left and right with an interval of more than 3 min between measurements. Before testing, mice were placed in a clear acrylic cylinder (15 cm high and 8 cm in diameter) for at least 30 min. The data represent the average latency of paw withdrawal for the right hind paw.

Electroencephalogram and Electromyogram Recordings

Electroencephalogram and electromyogram recordings were obtained as described previously.[24] Briefly, electroencephalogram signals were monitored with two stainless-steel electroencephalogram recording screws 1 mm anterior to the bregma or λ, both 1.5 mm lateral to the midline, and electromyogram activity was monitored by stainless steel, nonstick-coated wires placed bilaterally into both trapezius muscles. Electroencephalogram and electromyogram signals were amplified, filtered (0.5–30 Hz and 20–200 Hz, respectively), digitized at a sampling rate of 128 Hz, and recorded using SleepSign software (Kissei Comtec, Nagano, Japan), which was also used to automatically classify vigilance over 4-s epochs as wakefulness, rapid eye movement (REM) sleep, or non-REM sleep using standard criteria. Finally, defined sleep–wake stages were examined visually and corrected, if necessary. For each epoch, the electroencephalogram power density in the δ (0.75–4.0 Hz) and θ bands (6.25–9.0 Hz) and the integrated electromyogram value were displayed on a computer monitor. Electroencephalogram and electromyogram activities were monitored for 24 h at 7 days after sciatic nerve ligation. Recordings were started at 8:00 PM. Vehicle

(5% DMSO) or olanzapine (0.06 mg/kg, intraperitoneal administration) was injected every day at 8:00 AM.

Drugs

The drugs used in the current study were morphine hydrochloride (Daiichi-Sankyo, Tokyo, Japan), prochlorperazine maleate (Sigma–Aldrich, St. Louis, MO), clozapine (Wako Pure Chemical Industries, Osaka, Japan), olanzapine (Toronto Research Chemicals, Toronto, Ontario, Canada), telenzepine dihydrochloride hydrate (Sigma–Aldrich), ritanserin (Tocris Biotechnology, Ellisville, CA), pyrilamine maleate salt (Sigma–Aldrich), ketanserin tartrate (Wako Pure Chemical Industries), granisetron (Sigma–Aldrich), GR113808 (Sigma–Aldrich), haloperidol (Sigma–Aldrich), L745870 (Research Biochemicals International, Natick, MA), raclopride (Santa Cruz Biotechnology, Santa Cruz, CA), pirenzepine (Toronto Research Chemicals), and DL-trihexyphenidyl hydrochloride (Sigma–Aldrich).

Statistical Analysis

Data are expressed as the mean with SEM. The statistical significant of differences between the groups was assessed with one-way and two-way ANOVA followed by the Bonferroni multiple comparisons test or Student *t* test (unpaired, two-tailed). The concentration of the test compound that caused 50% inhibition of specific binding (IC_{50} value) was determined from each concentration-response curve. All statistical analyses and IC_{50} values were calculated by Prism software (version 5.0a, GraphPad Software). A P value of <0.05 was considered to reflect significance.

Results

Binding Properties of Clozapine

In mouse brain membranes, we determined the competitive displacement binding of [^{3}H]clozapine with graded concentrations (10^{-11}–10^{-4} M) of unlabeled clozapine, olanzapine, telenzepine, ritanserin, pyrilamine, ketanserin, GR113808, granisetron, haloperidol, L745870, and raclopride. The binding of [^{3}H]clozapine was displaced by olanzapine in a concentration-dependent manner (fig. 1A). In addition, the binding of [^{3}H]clozapine was partially displaced by telenzepine (M_1), ritanserin (5-HT_{2A}), pyrilamine (H_1), ketanserin (5-HT_{2C}), GR113808 (5-HT_4), granisetron (5-HT_3), haloperidol (D_2), L745870 (D_4), and raclopride (D_2) (fig. 1B).

Binding Properties of Olanzapine with 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_4, H_1, and M_1 Receptors

In mouse brain membranes, we determined the competitive displacement binding of [^{3}H]ketanserin, [^{3}H]BRL-43694 (granisetron), [^{3}H]pyrilamine, [^{3}H]GR113808, and [^{3}H]pirenzepine with graded concentrations (10^{-11}–10^{-4} M) of unlabeled ketanserin, granisetron, pyrilamine, GR113808, telenzepine, pirenzepine and olanzapine. The binding of [^{3}H]ketanserin and [^{3}H]pirenzepine was displaced by olanzapine in a concentration-dependent manner (fig. 2, A and B). The binding of [^{3}H]pyrilamine, [^{3}H]BRL-43694, and [^{3}H]GR113808 was partially displaced by olanzapine (fig. 2, C, D, and E).

Suppression of Morphine-induced Emesis by Olanzapine or Prochlorperazine

Pretreatment with either olanzapine (0.03 mg/kg, subcutaneous injection) 30 min before the injection of morphine (0.6 mg/kg, subcutaneous injection) or prochlorperazine (0.3 mg/kg and 1.0 mg/kg, subcutaneous injection) 60 min before the injection of morphine reduced the number of retching and vomiting behaviors induced by morphine (fig. 3).

Effects of Antipsychotics on Catalepsy

The results from the horizontal bar test as a measure of catalepsy were obtained at 15, 30, 45, and 60 min after the subcutaneous injection of vehicle, prochlorperazine (0.3–1 mg/kg), haloperidol (0.03–0.3 mg/kg), risperidone (0.01–0.1 mg/kg), or olanzapine (0.03–0.3 mg/kg). Although the catalepsy scores were not affected by a single subcutaneous injection of olanzapine (0.03–0.3 mg/kg), catalepsy was observed with the other antipsychotics within this dose range (fig. 4).

Effects of Olanzapine on the Morphine-induced Increase in the Concentrations of Dopamine and its Metabolites in Dialysate

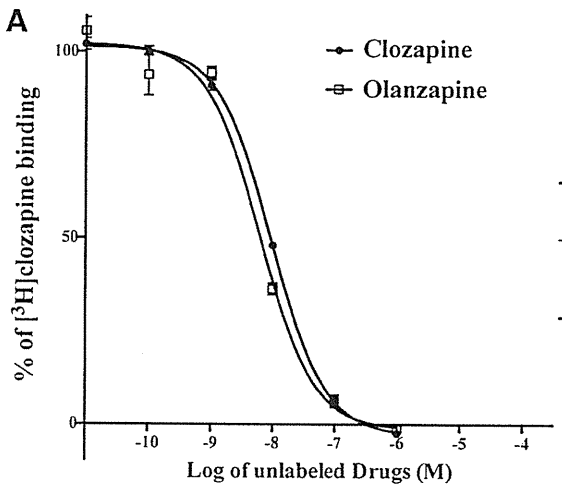
In the microdialysis study, the concentrations of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenyl acetic acid in dialysate from the rat nucleus accumbens were markedly increased by the intraperitoneal administration of morphine at 10 mg/kg compared with those under the administration of saline. The increased concentrations of dopamine, 3,4-dihydroxyphenylacetic acid, and 3-methoxy-4-hydroxyphenyl acetic acid in the nucleus accumbens after the administration of morphine were not affected by olanzapine at 0.3 mg/kg (olanzapine-morphine *vs.* vehicle-morphine: $F_{(1,77)} = 0.1516$, $P = 0.7086$ fig. 5A; $F_{(1,77)} = 0.06326$, $P = 0.8086$ fig. 5B; $F_{(1,77)} = 1.851$, $P = 0.2158$ fig. 5C).

Effect of Olanzapine on the Morphine-induced Inhibition of Gastrointestinal Transit

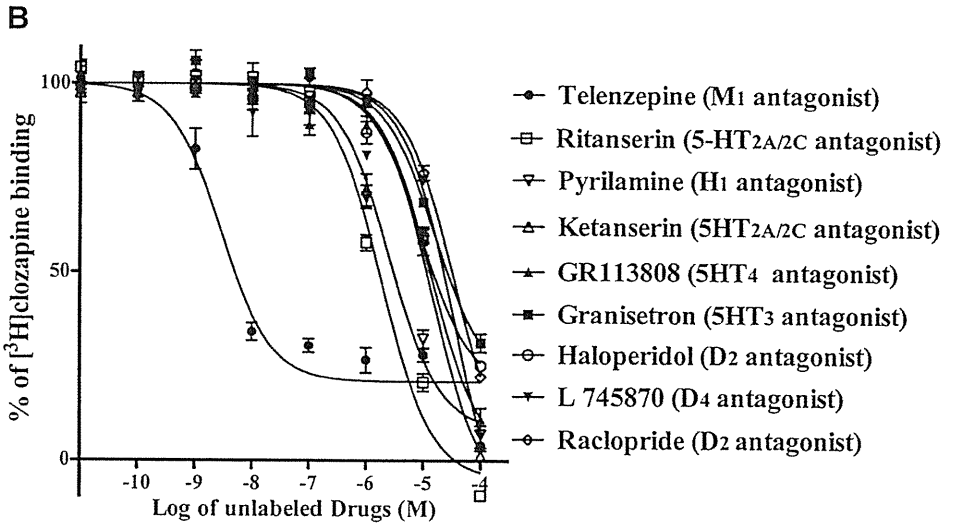
Morphine slowed gastrointestinal transit, and this effect was not significantly altered by the coadministration (subcutaneous injection) of olanzapine at 0.03–1 mg/kg (fig. 6A). Olanzapine itself did not slow gastrointestinal transit at doses of 0.03 and 0.1 mg/kg but significantly inhibited gastrointestinal transit at 0.3 and 1 mg/kg (fig. 6B).

Effects of Olanzapine on Blood Glucose

Blood glucose was measured after long-term treatment with olanzapine, saline, or vehicle (5% DMSO) in mice. Hypergly-



Antagonists	Clozapine	Olanzapine
IC50 (nM) for displacing [^{3}H]clozapine binding	9.56 (8.55-10.63)	6.26 (4.27-9.20)



Antagonists	IC50 (nM)
Telenzepine	2.91 (1.66-5.13)
Ritanserin	1885 (1368-2597)
Pyrilamine	2559 (1949-3339)
Ketanserin	> 10000
GR113808	> 10000
Granisetron	> 10000
Haloperidol	9127 (6329-13160)
L745870	> 10000
Raclopride	> 10000

Fig. 1. Displacement of the binding of [^{3}H]clozapine in membranes of mouse brain without the cerebellum by clozapine, olanzapine, telenzepine, ritanserin, pyrilamine, GR113808, granisetron, ketanserin, haloperidol, L745870, and raclopride. Experiments were performed in the presence of [^{3}H]clozapine (0.2 nM) and increasing concentrations of either clozapine or olanzapine (*A*) or of telenzepine, ritanserin, pyrilamine, GR113808, granisetron, ketanserin, haloperidol, L745870, or raclopride (*B*). The data represent the mean ± SEM of three to four samples. IC_{50} values were determined using an analysis of variance and linear regression techniques. To calculate the IC_{50} values, at least six drug doses were used, and three samples were used for each dose. Values in parentheses indicate the 95% confidence range.

cemia was not observed under treatment with olanzapine at 0.03, 0.1, or 0.3 mg/kg (subcutaneous injection) (fig. 7).

Thermal Hyperalgesia Induced by Sciatic Nerve Ligation in Mice

Sciatic nerve ligation markedly decreased the latency of paw withdrawal in response to a thermal stimulus on the ipsilateral side. This state of persistent pain caused by partial ligation of the sciatic nerve was suppressed by treatment with olanzapine at 0.06 mg/kg (fig. 8).

Changes in Sleep Vigilance in a Neuropathic Pain-like State Using Electroencephalogram and Electromyogram Recordings

We next investigated the changes in sleep patterns in sciatic nerve-ligated mice. Vigilance was classified automatically offline as wakefulness, REM sleep, or non-REM sleep. Mice with sciatic nerve ligation showed a statistically significant increase in wakefulness ($P = 0.0009$ *vs.* sham operated mice with vehicle, fig. 9A) and a decrease in non-REM sleep ($P = 0.0067$ *vs.* sham-operated mice with vehicle, fig. 9C) during the light phase. REM sleep during the light phase was not affected by sciatic nerve ligation ($P = 0.2896$ *vs.* sham-operated mice with vehicle, fig. 9B). On the other hand, there was no statistically significant difference in the sleep conditions during the dark phase between the two groups (wakefulness: $P = 0.6170$ *vs.* sham operated mice with vehicle, fig. 9D; REM: $P = 0.3936$ *vs.* sham operated mice with vehicle, fig. 9E; non-REM: $P = 0.5479$ *vs.* sham operated mice with vehicle, fig. 9F).

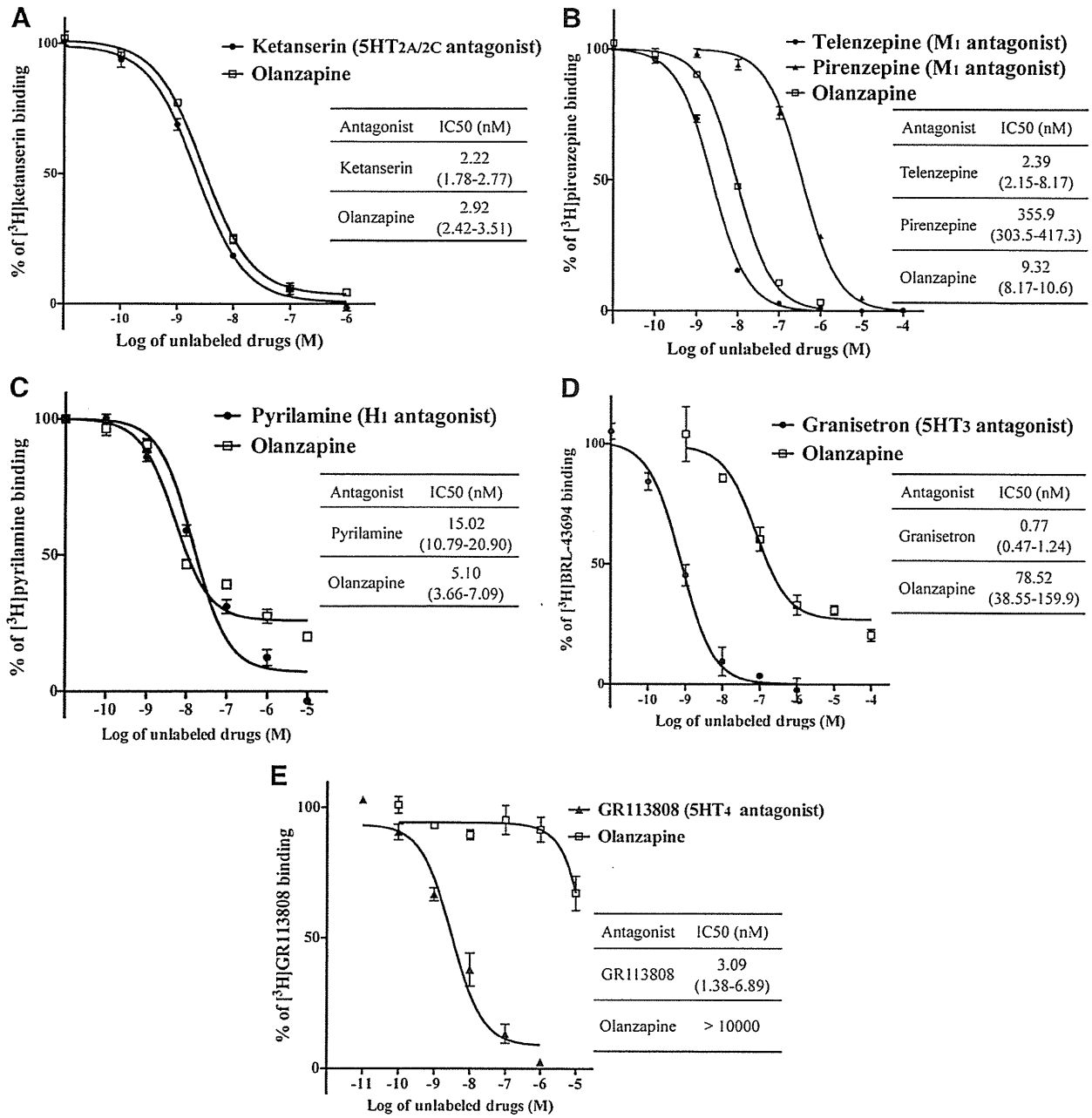


Fig. 2. Displacement of the binding of the serotonin (5-HT)$_{2A/C}$ receptor ligand [^{3}H]ketanserin (*A*), the muscarinic M_1 receptor ligand [^{3}H]pirenzepine (*B*), the H_1 receptor ligand [^{3}H] pyrilamine (*C*), the 5-HT_3 receptor ligand [^{3}H]BRL-43694 (granisetron) (*D*), or the 5-HT_4 receptor ligand [^{3}H]GR113808 (*E*) in membranes of mouse brain without the cerebellum by ketanserin, pirenzepine, telenzepine, pyrilamine, granisetron, GR113808, or olanzapine. Experiments were performed in the presence of [^{3}H]ketanserin (0.5 nM), [^{3}H]BRL-43694 (0.5 nM), [^{3}H]pyrilamine (0.5 nM), [^{3}H]GR113808 (0.5 nM), or [^{3}H]pirenzepine (0.5 nM) and increasing concentrations of ketanserin, granisetron, pyrilamine, GR113808, pirenzepine, telenzepine, or olanzapine. The data represent the mean ± SEM of three to four samples. IC_{50} values were determined using an analysis of variance and linear regression techniques. To calculate the IC_{50} values, at least six drug doses were used, and three samples were used for each dose. Values in parentheses indicate the 95% confidence range.

Changes in the Hypnotic Effects of Olanzapine in a Neuropathic Pain-like State Using Electroencephalogram and Electromyogram Recordings

To ascertain the hypnotic effect of olanzapine in a neuropathic pain-like state, we performed electroencephalogram and electromyogram recordings. The increased wakefulness and decreased non-REM during the light phase in nerve-ligated mice were significantly attenuated compared with those in sham-operated mice by the intraperitoneal administration of olanzapine (wakefulness: $P = 0.0006$ *vs.* nerve-

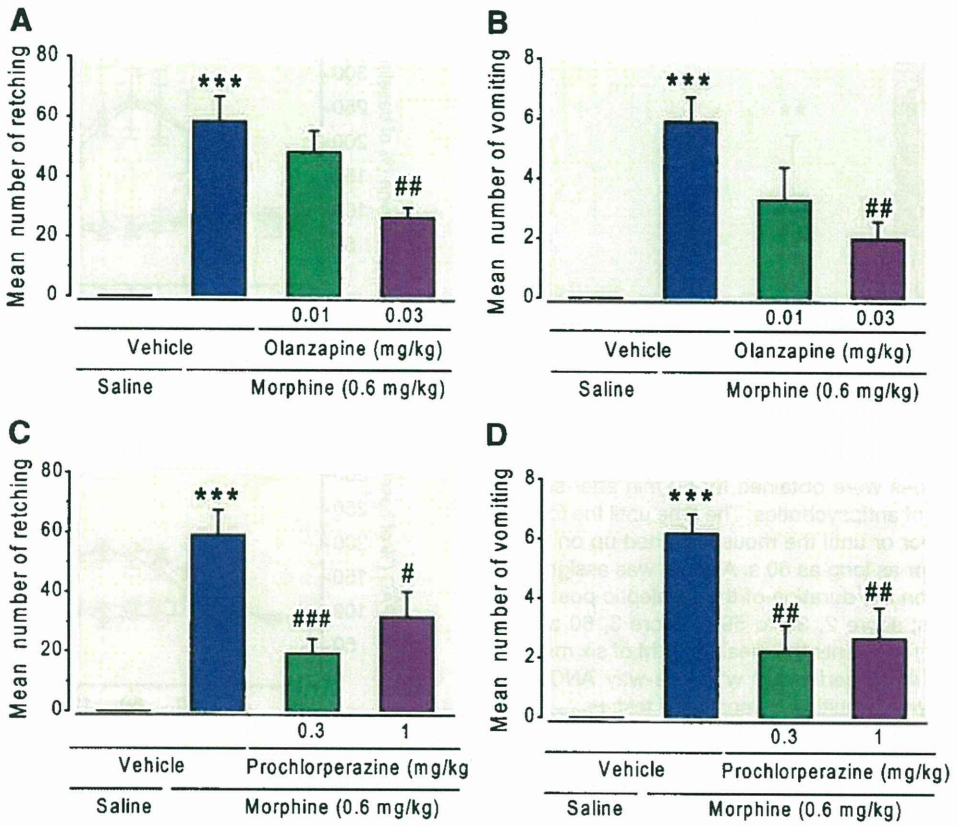


Fig. 3. Effects of olanzapine on subcutaneous injection morphine-induced retching (*A*, *C*) and vomiting (*B*, *D*) in ferrets. Groups of ferrets were pretreated with olanzapine (0.01 and 0.03 mg/kg, subcutaneous injection) (*A*, *B*), prochlorperazine (0.3 and 1.0 mg/kg, subcutaneous injection) (*C*, *D*), or vehicle before the administration of morphine (0.6 mg/kg, subcutaneous injection). Animals were observed for 30 min after subcutaneous injection of morphine. Each column represents the mean ± SEM of 9–10 ferrets. Statistical analyses were performed using one-way ANOVA followed by the Bonferroni multiple comparisons test: $F_{(3,39)} = 20.41$, $P < 0.0001$ (*A*); $F_{(3,39)} = 11.29$, $P < 0.0001$ (*B*); $F_{(3,37)} = 15.13$, $P < 0.0001$ (*C*); $F_{(3,37)} = 13.70$, $P < 0.0001$ (*D*). *** $P < 0.001$ *versus* vehicle-saline; ### $P < 0.001$; ## $P < 0.01$ or # $P < 0.05$ *versus* vehicle-morphine.

ligated mice with vehicle, fig. 9A; non-REM: $P = 0.001$ *vs.* nerve-ligated mice with vehicle, fig. 9C).

Discussion

The use of opioids for pain management is often associated with nausea and vomiting. Opioids induce emesis by stimulating the CTZ in the brainstem and by enhancing vestibular sensitivity.[25,26] Although several compounds are known to act on receptors in the CTZ, opioid-induced nausea and vomiting are attributable primarily to the transmission of dopamine. Many clinicians consider that typical antipsychotics such as prochlorperazine and haloperidol, which mainly act as dopamine D_2 receptor antagonists, are the drugs of choice for preventing the nausea and vomiting induced by morphine.[27–29] However, such compounds often produce extrapyramidal symptoms.[4]

Olanzapine is an atypical thienobenzodiazepine antipsychotic that is clinically indicated for schizophrenia and mania.[30] It blocks multiple neurotransmitters, including dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors.[31] In the current binding study, olanzapine showed the highest affinity for muscarinic M_1 receptors. To understand its affinity in greater detail, we investigated the affinity of olanzapine toward serotonin 5-$HT_{2A/2C}$, 5-HT_3, histamine H_1, dopamine D_2, dopamine D_4, and 5-HT_4 receptors. Olanzapine also showed affinity for each of these receptors. Because of its effect on several neurotransmitters that are associated with nausea and vomiting, we expected that olanzapine would have potential as an antiemetic medication. In a behavioral study, we found that morphine-induced nausea and vomiting were decreased in a dose-dependent manner by pretreatment with olanzapine at a dose that was almost 1/200 of that at which an antipsychotic effect is observed,[32] whereas olanzapine at a dose that had antiemetic effects failed to induce catalepsy. However, although the dopamine D_2 receptor antagonist prochlorperazine suppressed morphine-induced nausea and vomiting, it did so at a dose that caused a dose-dependent increase in the expression of catalepsy. Furthermore, olanzapine had no effect on the morphine-induced release of dopamine in the nucleus accumbens. Muscarinic M_1 receptors have been suggested to be responsible for the opioid-induced stimula-

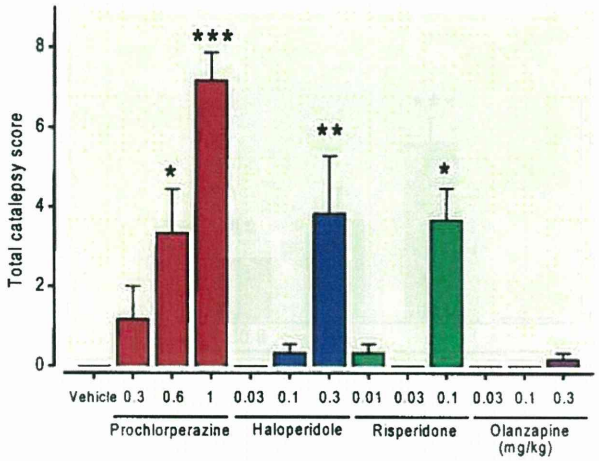


Fig. 4. Expression of catalepsy caused by antipsychotics in mice. Catalepsy values were obtained for 60 min after subcutaneous injection of antipsychotics. The time until the forepaw touched the floor or until the mouse climbed up on the bar was measured for as long as 60 s. A score was assigned to each test based on the duration of the cataleptic posture (score 1, 15 to 29 s; score 2, 30 to 59 s; score 3, 60 s or more). Each column represents the mean ± SEM of six mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test: $F_{(12,77)} = 12.59$, $P < 0.0001$. * $P < 0.05$, ** $P < 0.01$, or *** $P < 0.001$ *versus* vehicle.

tion of the vestibular apparatus.[6] In addition, sensory input from the vestibular apparatus to the vomiting center follows muscarinic M_1 receptor pathways. Taken together with the fact that olanzapine showed the highest affinity toward muscarinic M_1 receptors, these findings suggest that, although the exact mechanism by which olanzapine suppresses morphine-induced emesis remains unclear, muscarinic M_1 receptors may be a critical target for morphine-induced emesis. To prove our hypothesis, we next investigated whether the selective muscarinic M_1 receptor antagonist trihexyphenidyl could affect morphine-induced nausea and vomiting. Trihexyphenidyl significantly suppressed morphine-induced retching and vomiting in ferrets (data not shown), which indicates that M_1 receptors play an important role in the opioid-sensitive emetic pathway. However, trihexyphenidyl significantly enhanced the morphine-induced increase in the release of dopamine in the nucleus accumbens (data not shown). If we consider the risk of the overexcitation of dopamine transmission with the use of drug combinations, a specific M_1 receptor antagonist might not be a better choice as an adjunct agent in combination with opioids. Because olanzapine acts not only on muscarinic M_1 receptors, but also partly on histamine H_1 and dopamine D_2 receptors as an antagonist,[10] it is likely that olanzapine at a dose lower than that at which it has antipsychotic effects could be useful for strongly preventing opioid-induced emesis without severe side effects.

Constipation is another adverse effect of treatment with morphine. In the current study, olanzapine at doses that had antiemetic effects had no effect on the morphine-induced

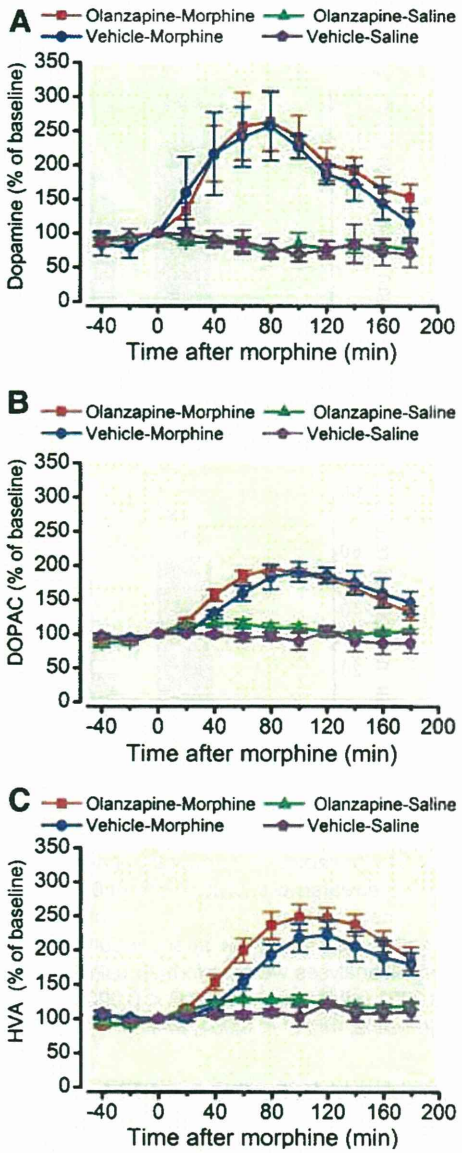


Fig. 5. Effect of olanzapine on the influence of intraperitoneal administration morphine on the dialysate concentrations of dopamine (*A*) and its metabolites (*B*, *C*) in the nucleus accumbens. After baseline fractions were collected, rats were pretreated with olanzapine (0.3 mg/kg, intraperitoneal administration) or vehicle 30 min before the injection of morphine (10 mg/kg, intraperitoneal administration) at time 0 to evoke the release of dopamine. Data are expressed as percentages of the corresponding baseline levels with SEM for three to five rats (number of rats: olanzapine-morphine, n = 5; vehicle-morphine, olanzapine-saline, n = 4; vehicle-saline, n = 3). Statistical analyses were performed with two-way ANOVA followed by the Bonferroni multiple comparisons test: vehicle-saline *versus* vehicle-morphine, $F_{(1,55)} = 19.48$, $P = 0.0069$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 0.1516$, $P = 0.7086$ olanzapine-morphine *versus* vehicle-morphine (*A*), $F_{(1,55)} = 32.57$, $P = 0.0023$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 0.06326$, $P = 0.8086$ olanzapine-morphine *versus* vehicle-morphine (*B*), $F_{(1,55)} = 23.42$, $P = 0.0047$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 1.851$, $P = 0.2158$ olanzapine-morphine *versus* vehicle-morphine (*C*).

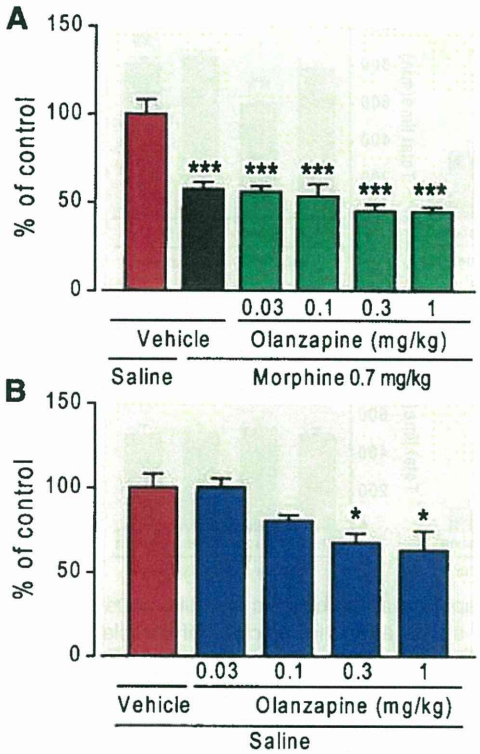


Fig. 6. Effect of pretreatment with olanzapine on the morphine-induced (*A*) inhibition of gastrointestinal transit and the effect of olanzapine itself (*B*). Each column represents the mean ± SEM of six mice. Ink was administered orally 20 min after the injection of morphine (0.7 mg/kg, subcutaneous injection) or saline, respectively. Groups of mice were pretreated with olanzapine (0.03–1 mg/kg, subcutaneous injection) at 30 min before the administration of morphine. Gastrointestinal transit was evaluated at 20 min after the oral administration of ink. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test: $F_{(5,35)} = 15.99$, $P < 0.0001$ (*A*); $F_{(4,29)} = 5.778$, $P = 0.0020$ (*B*). * $P < 0.05$, *** $P < 0.001$ *versus* vehicle-saline.

inhibition of gastrointestinal transit. This may be attributable to the high central transitivity of olanzapine.

Long-term treatment with olanzapine is most commonly associated with increased weight gain, obesity, and diabetes mellitus.[33] Therefore, we evaluated the effect of chronic treatment with olanzapine on blood glucose. As a result, hyperglycemia was not observed during treatment with olanzapine at a dose at which it had an antiemetic effect (0.03 mg/kg). However, long-term treatment with olanzapine at a dose of 1 mg/kg was associated with a slight but statistically significant increase in blood glucose concentrations. These findings support the idea that olanzapine may have a wide margin of safety when used as an antiemetic.

With regard to sleep disturbance in severe pain, we confirmed that mice with sciatic nerve ligation showed a statistically significant increase in wakefulness and a decrease in non-REM sleep during the light phase. Under the current conditions, treatment with olanzapine at doses at which the pain threshold was restored improved the sleep disturbance

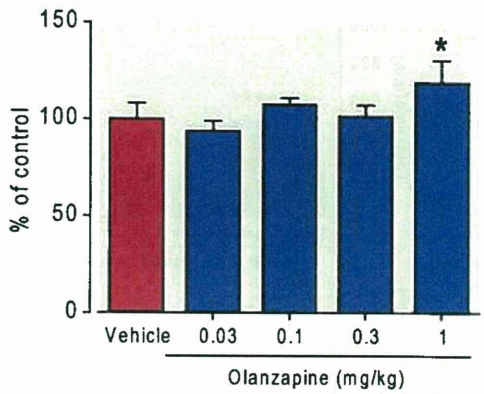


Fig. 7. Blood glucose concentrations after chronic treatment with olanzapine. Hyperglycemia was not observed in treatment with olanzapine (0.03, 0.1, or 0.3 mg/kg subcutaneous injection) for 7 days, whereas the glucose concentration was significantly increased by subcutaneous injection of olanzapine at 1 mg/kg. Values are expressed as a percentage of the control. Each column represents the mean ± SEM of four mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test. * $P < 0.05$ *versus* vehicle.

after sciatic nerve ligation. Histamine and serotonin are the key neurotransmitters that regulate wakefulness, and their receptors are the ultimate targets of many wakefulness- and sleep-promoting drugs. In particular, histamine H_1 receptor antagonist and serotonin 5-$HT_{2A/2C}$ receptor antagonist are known to shift one's arousal state from hyperactivity to sleep.[34] Therefore, the improvement of sleep disturbance during treatment with olanzapine may result from the

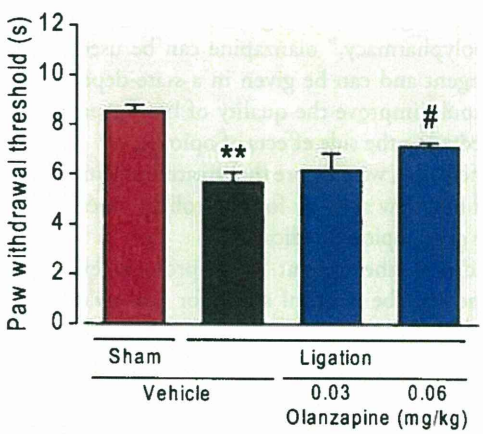


Fig. 8. Effect of olanzapine on thermal hyperalgesia induced by nerve ligation in mice. Groups of mice were injected with olanzapine (0.06 mg/kg, intraperitoneal administration) or vehicle at 7 days after sciatic nerve ligation or sham operation. Thermal hyperalgesia was measured 1 h after a single intraperitoneal administration of olanzapine or vehicle. Each column represents the mean ± SEM of six to eight mice (number of mice: sham-vehicle, n = 6; ligation-vehicle, ligation-olanzapine, n = 8). Statistical analyses were performed with Student *t* test. ** $P = 0.0017$ *versus* sham-vehicle. # $P = 0.031$ *versus* nerve ligation-vehicle.

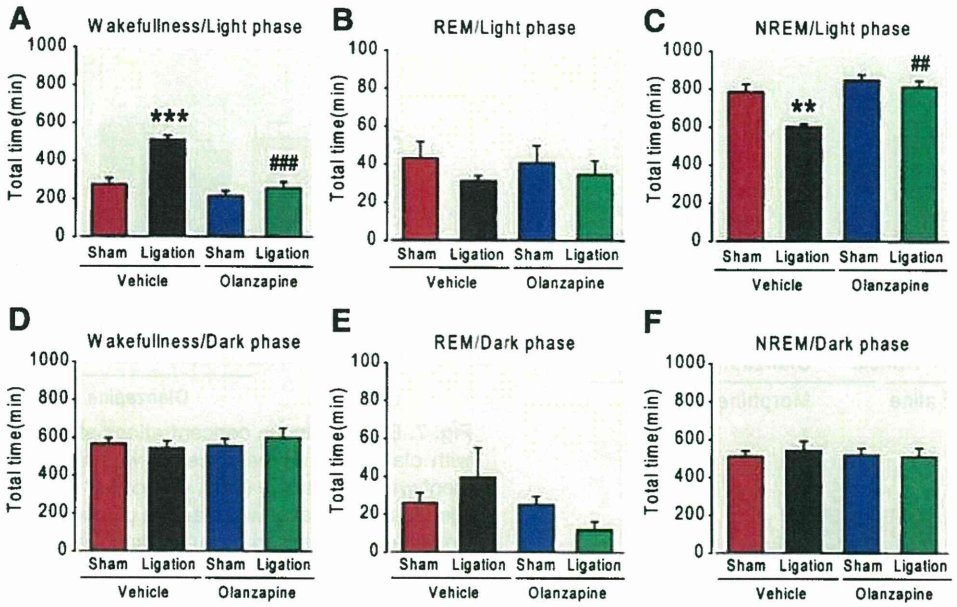


Fig. 9. Changes in sleep vigilance related to the hypnotic effects of olanzapine in a neuropathic pain-like state as determined by electroencephalogram and electromyogram recordings. Sleep–wake states after the injection of vehicle (5% dimethyl sulfoxide) or olanzapine at 7 days after sciatic nerve ligation. Vehicle or olanzapine (0.06 mg/kg, intraperitoneal administration) was injected once at 8:00 AM. The total time spent in wakefulness in the light phase (*A*) and the dark phase (*D*), rapid eye movement (REM) sleep in the light phase (*B*) and in the dark phase (*E*), and non-REM sleep in the light phase (*C*) and in the dark phase (*F*) was determined by electroencephalogram and electromyogram recording. Each column represents the mean ± SEM of five mice. Statistical analyses were performed with Student *t* test. ** $P = 0.0067$, *** $P = 0.0009$ *versus* sham-vehicle; ## $P = 0.001$, ### $P = 0.0006$ *versus* nerve ligation-vehicle.

agent's antagonistic effects toward histamine H_1 and serotonin 5-$HT_{2A/2C}$.

Overall, the current results suggest that olanzapine may be useful for the treatment of morphine-induced emesis, reducing neuropathic pain, and improving pain-related sleep disturbance. Against a background of increasing concern about "polypharmacy," olanzapine can be used as a single adjunct agent and can be given in a state-dependent dose, which should improve the quality of life for patients while greatly reducing the side effects of opioids.

In conclusion, we propose that treatment with olanzapine may lead to a new strategy for controlling emesis when patients are given opioid medications.

In addition, the current study provides evidence that olanzapine may be a useful agent for improving the sleep disturbance caused by neuropathic pain that is observed in some patients with cancer.

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