

## Differential interactions of traditional and novel antiemetics with dopamine D<sub>2</sub> and 5-hydroxytryptamine<sub>3</sub> receptors

Anne Hamik and Stephen J. Peroutka

Department of Neurology, Stanford University Medical Center, Stanford, CA 94305, USA

**Summary.** The affinities of 11 drugs for both dopamine D<sub>2</sub> and 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor sites were determined in brain membranes. The five “traditional” antiemetics (chlorpromazine, prochlorperazine, droperidol, fluphenazine, and domperidone) displayed high affinity (<20 nM) for dopamine D<sub>2</sub> receptors in corpus striatum but were inactive at 5-HT<sub>3</sub> receptors. In contrast, five recently developed 5-HT<sub>3</sub> antagonists (BRL 43694, ICS 205-930, zacopride, Lilly 278584, and MDL 72222) displayed nanomolar affinity for the 5-HT<sub>3</sub> site but were inactive (>10,000 nM) at the dopamine D<sub>2</sub> receptor. Metoclopramide was unique among these agents in that it was similarly potent at dopamine D<sub>2</sub> (240 ± 60 nM) and 5-HT<sub>3</sub> (120 ± 30 nM) receptors.

### Introduction

Nausea and vomiting resulting from cancer chemotherapy are common side effects that can cause patients to refuse subsequent chemotherapeutic sessions [19]. However, against certain types of chemotherapy- or radiation-induced nausea and vomiting, traditional antiemetics such as dopamine D<sub>2</sub> receptor antagonists [27, 30, 33] are only minimally effective. Moreover, dopamine D<sub>2</sub> antagonists often cause side effects such as extrapyramidal symptoms, which further restrict their usefulness [3, 17, 21].

A new class of pharmacological agents has recently been developed that appears to possess uniquely potent and effective antiemetic activity [24]. These drugs have been designated 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonists and include drugs such as ICS 205-930 and MDL 72222 [12, 28]. Metoclopramide, traditionally considered to be a dopaminergic antagonist, has also been reported to have 5-HT<sub>3</sub> receptor antagonist properties [13, 22]. In animals, 5-HT<sub>3</sub> antagonists block both cytotoxic drug- and radiation-induced emesis [1, 6, 11, 22–24, 31]. These drugs also appear to abolish nausea and vomiting in patients receiving cytotoxic drugs [4, 10, 20]. In the present study, a series of five traditional dopamine D<sub>2</sub> antagonists, five recently developed 5-HT<sub>3</sub> antagonists, and metoclopramide were analyzed at both dopamine D<sub>2</sub> and 5-HT<sub>3</sub> receptor binding sites in brain membranes.

Offprint requests to: S. J. Peroutka

### Material and methods

Radioligand-binding studies were carried out according to the methods of Ison and Peroutka [18] and Peroutka and Hamik [26]. Frozen rat brains (Pel Freez Biologicals; Rogers, Ark) were thawed from –20° C and dissected. Tissue was homogenized in 20 vol. 50 mM TRIS (pH 7.7 at 25° C) for [<sup>3</sup>H]-spiperone binding or Krebs-HEPES buffer for [<sup>3</sup>H]-quipazine assays and centrifuged at 49,000 g for 10 min. Cortical tissue was used for [<sup>3</sup>H]-quipazine binding and corpus striatum, for [<sup>3</sup>H]-spiperone binding. The supernatant was discarded and the pellet resuspended in the same volume of buffer. After a 10-min incubation at 37° C, the tissue was again centrifuged. The final pellet was resuspended in 80 vol. assay buffer. For dopamine binding ([<sup>3</sup>H]-spiperone + 40 nM ketanserin [25]), the assay buffer consisted of 10<sup>-5</sup> M pargyline, 4 mM CaCl<sub>2</sub>, and 0.1% ascorbate in 50 mM TRIS. [<sup>3</sup>H]-Quipazine binding was carried out in a Krebs-HEPES buffer that consisted of 25 mM HEPES, 120 mM NaCl, 2.5 mM CaCl<sub>2</sub>, 4.8 mM KCl, and 1.2 mM MgCl<sub>2</sub> (pH adjusted to 7.4).

Binding assays consisted of 0.1 ml [<sup>3</sup>H]-ligand, 0.1 ml buffer or displacing drug, and 0.8 ml tissue homogenate. Following a 30-min incubation at 25° C, the assays were rapidly filtered under vacuum through #32 glass-fiber filters (Schleicher and Schuell; Keene, NH) with two 5-ml washes using 50 mM TRIS buffer. Radioactivity was measured by liquid scintillation spectroscopy in 2.5 ml scintillation cocktail (Research Products International; Mt. Prospect, Ill) at 61% efficiency. All experiments were carried out in triplicate and repeated 3–6 times. Specific binding was defined as the excess over blanks taken in the presence of 10<sup>-6</sup> M (+)butaclamol for [<sup>3</sup>H]-spiperone binding and 10<sup>-7</sup> M ICS 205-930 for [<sup>3</sup>H]-quipazine binding. Generally, 75% of the [<sup>3</sup>H]-spiperone binding and 40% of the [<sup>3</sup>H]-quipazine binding was specific.

Drugs were prepared for experiments as follows: endo-*N*-(9-methyl-9-azabicyclo-[3,2,1]non-3-yl)-1-methyl-1*H*-indazole-3-carboxamide (BRL 43694), (3*a*-tropanyl)-1*H*-indole-3-carboxylic acid ester (ICS 205-930), zacopride, 1-methyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-indazole-3-carboxamide (Lilly 278584), and metoclopramide were dissolved in assay buffer; 1*aH*,3*a*,5*aH*-tropan-3-yl-3,5-dichlorobenzoate (MDL 72222), chlorpromazine, and ketanserin were dissolved in dH<sub>2</sub>O and then diluted in assay buffer; (+)butaclamol, droperidol, and fluphenazine were dissolved in 25%–50% EtOH at

$10^{-3}$  M and then diluted in buffer; and domperidone and prochlorperazine were dissolved in 25% 1 M acetic acid and diluted in assay buffer.

Drugs and chemicals were obtained from the following sources: [ $^3$ H]-quipazine (52.3 Ci/mmol) and [ $^3$ H]-spiperone (21.4 Ci/mmol), Dupont New England Nuclear (Boston, Mass); BRL 43694, Beecham (Betchworth, England); ICS 205-930, Sandoz Pharmaceuticals (East Hanover, NJ); zacopride, A. H. Robins (Richmond, Va); Lilly 278584, Lilly Research Laboratories (Indianapolis, Ind); metoclopramide, chlorpromazine, TRIS-HCl, HEPES, and pargyline, Sigma Chemical Co. (St. Louis, Mo); prochlorperazine, Smith Kline and French (Philadelphia, Pa); droperidol, domperidone, and ketanserin, Janssen Pharmaceutica (New Brunswick, NJ); (+)butaclamol, Research Biochemicals Inc. (Wayland, Mass); CaCl<sub>2</sub>, Fisher Scientific (Phillipsburg, NJ); ascorbic acid and NaCl, Mallinckrodt (Paris, Ky); and MgCl<sub>2</sub> and KCl, J. T. Baker Chemical Co. (Phillipsburg, NJ).

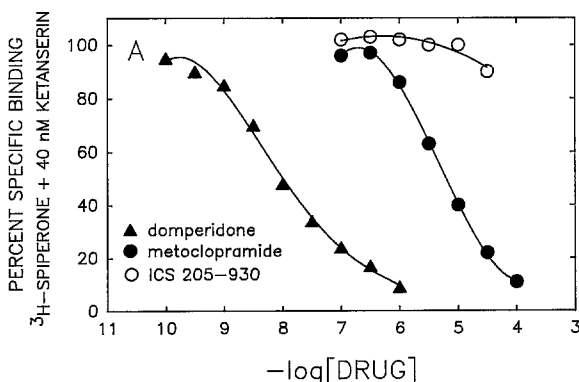
## Results

### Drug interaction with D<sub>2</sub> receptors

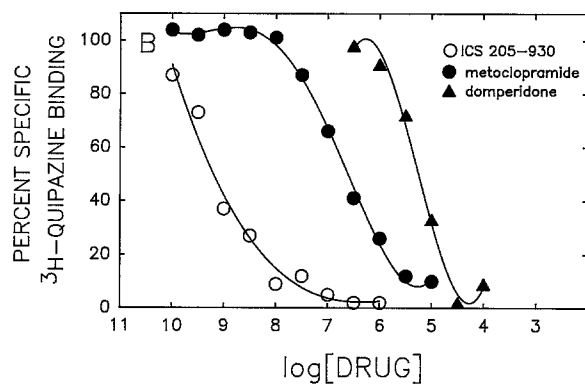
The results of drug competition studies are given in Table 1. The traditional antiemetics were, as previously reported [18], quite potent at the dopamine D<sub>2</sub> site; K<sub>i</sub> values ranged from  $2.4 \pm 0.6$  nM for droperidol to  $18 \pm 5$  nM for chlorpromazine. Metoclopramide demonstrated a K<sub>i</sub> value of  $240 \pm 60$  nM ( $n = 10$ ). By contrast, putative 5-HT<sub>3</sub> antagonists were inactive at the dopamine D<sub>2</sub> site in the rat corpus striatum. BRL 43694, ICS 205-930, zacopride, Lilly 278584, and MDL 72222 all demonstrated K<sub>i</sub> values of  $> 10,000$  nM. Representative drug competition curves for ICS 205-930, metoclopramide, and domperidone against specific dopamine D<sub>2</sub> receptors are shown in Fig. 1A.

### Drug interactions with 5-HT<sub>3</sub> receptors

Drug affinities were determined at 5-HT<sub>3</sub> membrane-recognition sites labeled by [ $^3$ H]-quipazine. Of the 11 drugs analyzed, 4 demonstrated less than nanomolar affinity for the 5-HT<sub>3</sub> site. These drugs (BRL 43694, ICS 205-930, za-



**Fig. 1A.** Drug competition studies vs specific [ $^3$ H]-spiperone + 40 M ketanserin binding in rat corpus striatum. Radioligand-binding assays were carried out as described in *Materials and methods*. Nonspecific binding was determined in the presence of 1  $\mu$ M (+) butaclamol. Data shown are the results of a single experiment carried out in triplicate. Each experiment was repeated 3–6 times



**Fig. 1B.** Drug competition studies vs specific [ $^3$ H]-quipazine binding in rat cortical membranes. Radioligand-binding assays were carried out as described in *Materials and methods*. Nonspecific binding was determined in the presence of 100 nM ICS 205-930. Data shown are the results of a single experiment carried out in triplicate. Each experiment was repeated 3–6 times

**Table 1.** Drug affinities for 5-HT<sub>3</sub>- and dopamine D<sub>2</sub>-labeled sites in rat brain membranes

Drug	Potency at 5-HT <sub>3</sub> Receptors K <sub>i</sub> (nM)	Potency at D <sub>2</sub> Receptors K <sub>i</sub> (nM)	Ratio 5-HT <sub>3</sub> /D <sub>2</sub>
Dopamine drugs:			
Prochlorperazine	$1,800 \pm 300$	$7.3 \pm 1$	200
Chlorpromazine	$1,900 \pm 200$	$18 \pm 5$	100
Droperidol	$4,200 \pm 30$	$2.4 \pm 0.6$	2,000
Fluphenazine	$> 10,000$	$4.8 \pm 3$	$> 2,000$
Domperidone	$> 10,000$	$12 \pm 3$	$> 800$
5-HT <sub>3</sub> drugs:			
BRL 43694	$0.30 \pm 0.04$	$> 10,000$	$< 0.001$
ICS 205-930	$0.38 \pm 0.02$	$> 10,000$	$< 0.001$
Zacopride	$0.42 \pm 0.2$	$> 10,000$	$< 0.001$
Lilly 278584	$0.52 \pm 0.2$	$> 10,000$	$< 0.001$
MDL 72222	$9.20 \pm 1.0$	$> 10,000$	$< 0.002$
Mixed drug:			
Metoclopramide	$120 \pm 30$	$240 \pm 60$	0.5

Radioligand-binding studies were carried out as described in *Materials and methods*. Values represent the mean  $\pm$  SE of 3–6 experiments carried out in triplicate

copride, and Lilly 278584) were essentially equipotent at the 5-HT<sub>3</sub> site, with K<sub>i</sub> values ranging from 0.30 to 0.52 nM. MDL 72222 was slightly less potent, with a K<sub>i</sub> value of  $9.2 \pm 1$  nM. Metoclopramide was the only traditional antiemetic that displayed less than micromolar affinity for the 5-HT<sub>3</sub> site, with a K<sub>i</sub> value of  $120 \pm 30$  nM. In contrast, the remainder of the traditional antiemetics were significantly less potent, with K<sub>i</sub> values ranging from  $1,800 \pm 300$  nM for prochlorperazine to  $> 10,000$  nM for fluphenazine and domperidone. Representative drug competition curves are shown in Fig. 1B.

## Discussion

The major finding of the present study is that the 11 drugs tested showed differential interactions with dopamine D<sub>2</sub> and 5-HT<sub>3</sub> receptor sites. The 5-HT<sub>3</sub> antagonists, although showing nanomolar affinity for central 5-HT<sub>3</sub> recognition sites, were inactive at dopamine D<sub>2</sub> receptor sites. Conver-

sely, the traditional antiemetics showed high affinity for the dopamine D<sub>2</sub> site. With the exception of metoclopramide, these drugs were approximately 100–2,000 times more potent at the D<sub>2</sub> site than at the 5-HT<sub>3</sub> site. Metoclopramide appeared to be similarly potent at D<sub>2</sub> and 5-HT<sub>3</sub> sites, a unique finding among the 11 drugs tested.

The antiemetic efficacy of various drugs, including dopamine D<sub>2</sub> antagonists, antihistamines, anticholinergics, and corticosteroids has been well documented [14, 15, 30, 32–34]. Unfortunately, these traditional antiemetics provide only modest relief from nausea and vomiting in patients undergoing therapy with most chemotherapeutic drugs; they are of extremely limited value with agents such as cisplatin, doxorubicin, and dacarbazine, which induce severe nausea and vomiting. Of particular interest is the claim that high-dose metoclopramide is the most effective agent currently available for the treatment of adverse effects caused by these regimens [33].

In contrast, 5-HT<sub>3</sub> antagonists (MDL 72222, ICS 205-930, BRL 24924, and GR38032F) are a recently developed group of drugs that have been shown to be potent antiemetics in ferrets receiving cisplatin and total-body radiation [6, 7, 8, 22–24, 31]. In recent human trials, the 5-HT<sub>3</sub> antagonists GR38032F [10], ICS 205-930 [20], and BRL 43694 [4] provided excellent relief from chemotherapy-induced nausea and vomiting. For example, 14 of 15 patients did not experience nausea or vomiting when given GR38032F along with cytotoxic drugs [10]. The only adverse effects were headache and mild sedation with ICS 205-930 and dry mouth and mild sedation with GR38032F. Therefore, 5-HT<sub>3</sub> antagonists appear to be extremely effective antiemetics when given with strongly emetic anticancer agents.

The mechanism(s) by which the drugs examined in this study relieve nausea and vomiting are not completely known [2]. Specific dopamine D<sub>2</sub> antagonists are thought to act via central dopamine antagonism in the chemoreceptor trigger zone [15]. Metoclopramide is thought to act at the cortex as well as with receptors in the periphery, where it induces gastric motility and emptying [16, 29]. This peripheral action may be explained in part by antagonism of dopamine D<sub>2</sub> receptors. However, since the role of dopamine in the control of gut motility seems minor, other mechanisms must exist through which metoclopramide exerts these effects [29]. It seems likely that this drug interacts with 5-HT<sub>3</sub> receptors located in the enteric system, and it may mediate gastric effects through this mechanism. In addition, since metoclopramide has relatively high affinity for 5-HT<sub>3</sub> recognition sites in rat brain tissues, some of its antiemetic effects may be due to its interactions with these CNS sites.

The antiemetic effects of the 5-HT<sub>3</sub> antagonists appear to be a consequence of 5-HT<sub>3</sub> blockade; however, whether this is due to largely peripheral actions or to both peripheral and central interaction with the receptor remains unclarified. For example, at small doses BRL 24924 (a potent stimulant of gastric motility [5]) mimics abdominal vagotomy in total-body-irradiated ferrets; that is, retching and vomiting is delayed by 30 min. Higher doses of BRL 24924 almost eliminate retching and vomiting for the entire 90-min test period [1]. These results were interpreted as indicating that BRL 24924 may, in addition to its probable action at the abdominal vagi, have an important effect in another area of the body.

In addition to their direct effect on 5-HT transmission, the 5-HT<sub>3</sub> antagonists may also have some modulatory effects on the dopaminergic system. A potent and highly selective 5-HT<sub>3</sub> antagonist, GR38032F, has been shown to modulate hyperactivity resulting from dopamine administration to rats and marmosets [9]. GR38032F was hypothesized to work by interrupting a 5-HT-dopamine-5-HT loop by which 5-HT serves to facilitate dopaminergic transmission. Perhaps a similar interaction between 5-HT and dopamine transmission is involved in the reduction of nausea and vomiting by 5-HT<sub>3</sub> antagonists.

However, the *direct* antagonism of dopamine D<sub>2</sub> receptors does not appear to be necessary for effective antiemetic treatment. Metoclopramide, which is significantly less potent at dopamine D<sub>2</sub> receptors than are the other traditional dopamine D<sub>2</sub> antiemetic agents, has also been shown to be the most effective antiemetic of the group [33]. Recent trials suggest that the 5-HT<sub>3</sub> antagonists are at least as effective as metoclopramide in reducing or eliminating nausea and vomiting resulting from chemotherapy. Thus, it is not apparent that the dopamine D<sub>2</sub> antiemetic effects of metoclopramide are a necessary component of its antiemetic efficacy; its 5-HT<sub>3</sub> antagonism alone may be sufficient to control emesis effectively.

Finally, radioligand-binding studies may be used as a screening tool for the selection of clinically useful drugs. For example, in the present study, two of the 5-HT<sub>3</sub> antagonists (zacopride and Lilly 278584) were not shown to have antiemetic effects. These drugs showed a binding pattern similar to those of the demonstrated antiemetics ICS 205-930, MDL 72222, and BRL 43694; that is, high affinity for the 5-HT<sub>3</sub> site in cortical tissue and inactivity at the dopamine D<sub>2</sub> site in corpus striatum. Zacopride shows an affinity for the 5-HT<sub>3</sub> site similar to that of BRL 43694. Lilly 278584 is more potent at the site than is MDL 72222. Thus, we would predict that both of these drugs would be effective in reducing emesis caused by agents such as cisplatin or by total-body radiation.

In summary, this study demonstrates that affinities of drugs to 5-HT<sub>3</sub> and dopamine D<sub>2</sub> sites correlates with their efficacy as antiemetics. Metoclopramide is superior to the other traditional agents in its antiemetic action and is also the only traditional agent that displays moderate affinity for 5-HT<sub>3</sub> receptors. Clinical trials with the 5-HT<sub>3</sub> antagonists MDL 72222, ICS 205-930, BRL 43694, and GR38032F have shown them to be at least equal to, and probably superior to, metoclopramide in antiemetic efficacy. These data indicate that the 5-HT<sub>3</sub> receptor plays a novel and important role in the pathophysiology of nausea and vomiting.

## References

1. Andrews PLR, Hawthorn J (1987) Evidence for an extra-abdominal site of action for the 5-HT<sub>3</sub> receptor antagonist BRL24924 in the inhibition of radiation-evoked emesis in the ferret. *Neuropharmacology* 26: 1367
2. Andrews PLR, Rapeport WG, Sanger GJ (1988) Neuropharmacology of emesis induced by anti-cancer therapy. *TIPS* 9: 334
3. Arrowsmith J, Gams RA (1981) Dystonia with droperidol therapy. *New Engl J Med* 305: 227
4. Carmichael J, Cantwell BMJ, Edwards CM, Rapeport WG, Harris AL (1988) The serotonin type 3 receptor antagonist BRL 43694 and nausea and vomiting induced by cisplatin. *Br Med J* 297: 110

5. Cooper SM, McClelland CM, McRitchie B, Turner DH (1986) BRL 24924: a new and potent gastric motility stimulant. *Br J Pharmacol [Suppl]*: 383, volume 88
6. Costall B, Domeney AM, Naylor RJ, Tattersall FD (1986) 5-Hydroxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis. *Neuropharmacology* 25: 959
7. Costall B, Kelly ME, Naylor RJ, Tan CCW, Tattersall FD (1986) 5-Hydroxytryptamine M-Receptor antagonism in the hypothalamus facilitates gastric emptying in the guinea-pig. *Neuropharmacology* 25: 1293
8. Costall B, Domeney AM, Gunning SJ, Naylor RJ, Tattersall FD, Tyers MB (1987) GR38032F: a potent and novel inhibitor of cisplatin-induced emesis in the ferret. *Br J Pharmacol [Suppl]*: 90, volume 90
9. Costall B, Domeney AM, Naylor RJ, Tyers MB (1987) Effects of the 5-HT<sub>3</sub> receptor antagonist, GR38032F, on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. *Br J Pharmacol* 92: 881
10. Cunningham D, Pople A, Ford HT, Hawthorn J, Gazet JC, Challoner T, Coombes RC (1987) Prevention of emesis in patients receiving cytotoxic drugs by GR38032F, a selective 5-HT<sub>3</sub> receptor antagonist. *Lancet* I: 1461
11. De Haan LD, De Mulder PHM, Beex LVAM, Debruyne FMJ, Challoner T, De Pauw BE (1988) The efficacy of GR38032F, an antagonist of 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) in the prophylaxis of cisplatin (CDDP)-induced nausea and vomiting. *Eur J Clin Oncol* 8: 1383
12. Fozard JR (1984) MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. *Nauyn-Schmiedeberg Arch Pharmacol* 326: 36
13. Fozard JR (1987) 5-HT<sub>3</sub> receptors and cytotoxic drug-induced vomiting. *TIPS* 8: 44
14. Gralla RJ, Itri LM, Pisko SE, Squillante AE, Kelsen DP, Braun DW, Bordin LA, Braun TJ, Young CW (1981) Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *New Engl J Med* 305: 905
15. Gralla RJ, Tyson LB, Bordin LA, Clark RA, Kelsen DP, Kris MG, Kalman LB, Groshen S (1984) Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treat Rep* 68: 163
16. Harrington RA, Hamilton CW, Brogden RN, Linkewich JA, Romankiewicz JA, Heel RC (1983) Metoclopramide: an updated review of its pharmacological properties and clinical use. *Drugs* 25: 451
17. Indo T, Ando K (1982) Metoclopramide-induced parkinsonism: clinical characteristics of ten cases. *Arch Neurol* 39: 494
18. Ison PJ, Peroutka SJ (1986) Neurotransmitter receptor binding studies predict antiemetic efficacy and side effects. *Cancer Treat Rep* 70: 637
19. Laszlo J, Lucas VS Jr (1981) Emesis as a critical problem in chemotherapy. *New Engl J Med* 305: 948
20. Leibundgut U, Lancranjan I (1987) First results with ICS 205-930 (5-HT<sub>3</sub> receptor antagonist) in prevention of chemotherapy-induced emesis. *Lancet* I: 1198
21. Leopold NA (1984) Prolonged metoclopramide-induced dyskinetic reaction. *Neurology* 34: 238
22. Miner WD, Sanger GJ (1986) Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol* 88: 497
23. Miner WD, Sanger GJ, Turner DH (1986) Comparison of the effect of BRL 24924, metoclopramide and domperidone on cisplatin-induced emesis in the ferret. *Br J Cancer [Suppl]* 1: 374
24. Miner WD, Sanger GJ, Turner DH (1987) Evidence that 5-hydroxytryptamine receptors mediate cytotoxic drug- and radiation-evoked emesis. *Br J Cancer* 56: 159
25. Norman AB, Battaglia G, Creese I (1987) Differential recovery rates of rat D<sub>2</sub> dopamine receptors as a function of aging and chronic reserpine treatment following irreversible modification: a key to receptor regulatory mechanisms. *J Neurosci* 7: 1484
26. Peroutka SJ, Hamik A (1988) [<sup>3</sup>H]Quipazine labels 5-HT<sub>3</sub> recognition sites in rat cortical membranes. *Eur J Pharmacol* 148: 297
27. Peroutka SJ, Snyder SH (1982) Antiemetics: neurotransmitter receptor binding predicts therapeutic actions. *Lancet* I: 658
28. Richardson BP, Engel G (1986) The pharmacology and function of 5-HT<sub>3</sub> receptors. *Trends Neurosci* 7: 424
29. Schulze-Delrieu K (1981) Metoclopramide. *New Engl J Med* 305: 28
30. Seigel LJ, Longo DL (1981) The control of chemotherapy-induced emesis. *Ann Intern Med* 95: 352
31. Stables R, Andrews PLR, Bailey HE, Costall B, Gunning SJ, Hawthorn J, Naylor RJ, Tyers MB (1987) Antiemetic properties of the 5HT<sub>3</sub>-receptor antagonist GR38032F. *Cancer Treat Rev* 14: 333
32. Strum SB, McDermed JE, Opfell RW, Riech LP (1982) Intravenous metoclopramide: an effective antiemetic in cancer chemotherapy. *JAMA* 247: 2683
33. Triozzi PL, Laszlo J (1987) Optimum management of nausea and vomiting in cancer chemotherapy. *Drugs* 34: 136
34. Wampler G (1983) The pharmacology and clinical effectiveness of phenothiazines and related drugs for managing chemotherapy-induced emesis. *Drugs* 25 [Suppl 1]: 35

Received 15 November 1989/Accepted 10 March 1989