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Chemotherapeutic agents do not interact with neurotransmitter receptors

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Summary. The interactions of cisplatin, 5-fluorouracil, doxorubicin, mitomycin, carmustine (BCNU), cyclophosphamide, methotrexate and thio-TEPA were assessed at three neurotransmitter receptor binding sites. Each drug was inactive at concentrations as high as 10^{-4} *M* in displacing the specific binding of ^{3}H-spiperone to dopamine D_2, ^{3}H-pyrilamine to histamine H_1, and ^{3}H-quinuclidinyl benzilate to muscarinic cholinergic receptors. These data suggest that chemotherapy-induced nausea and vomiting are not due to interactions with neurotransmitter receptors.

Introduction

Nausea and vomiting secondary to chemotherapeutic agents are a major cause of morbidity in cancer therapy [1]. Gastrointestinal upset occurs in most patients treated with drugs such as cisplatin and may be the most debilitating side-effect of the therapy. Nausea and vomiting may actually limit the course of chemotherapy in many patients [3]. However, the mechanism of action by which chemotherapeutic agents produce these side-effects is unknown. While it has been postulated that drugs such as 5-fluorouracil act directly on the chemoreceptor trigger zone in the central nervous system, drugs such as cisplatin are believed to induce emesis via peripheral effects [3].

By contrast, the efficacy of many antiemetic agents appears to derive from their ability to block dopamine D_2, histamine H_1, and/or muscarinic cholinergic receptors [2]. Moreover, these neurotransmitter receptors have been identified in brainstem pathways (e.g., area postrema) that are believed to mediate nausea and vomiting [2]. In addition, these neurotransmitter receptors are also present outside the central nervous system [4]. Conceivably, chemotherapeutic agents may also interact with the same neurotransmitter receptor sites as are blocked by classical antiemetics. Therefore, the present study was conducted to evaluate whether several commonly used chemotherapeutic agents could compete for radioligand binding to specific neurotransmitter receptor sites.

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Materials and methods

Radioligand studies were performed in brain membranes as previously described [2]. Adult rat brains were obtained from Pel-Freez Biologicals (Rogers, Ark) and stored at −20 °C until needed. On the day of study, the brains were defrosted, and the cortex and caudate were dissected. Tissues were homogenized in 20 vol. 50 m*M* Tris-HCl (pH 7.7 at 25 °C) using a Brinkmann Polytron and then centrifuged in an IEC B20A centrifuge at 49000 *g* for 10 min. The supernatant was discarded, and the pellet was resuspended in the same volume of Tris-HCl buffer and incubated at 37 °C for 10 min prior to a second 10-min centrifugation at 49000 *g*. The final pellet was resuspended in 80 vol. Tris-HCl buffer containing 10 μ*M* pargyline, 4 m*M* calcium chloride, and 0.1% ascorbic acid. The suspensions were immediately used in the binding assay.

Binding assays for drug displacement studies consisted of 0.1 ml ^{3}H-ligand [final concentrations: 0.6–0.8 n*M* ^{3}H-spiperone; 1.5–2.0 n*M* ^{3}H-pyrilamine; 0.3–0.4 n*M* ^{3}H-quinuclidinyl benzilate (QNB)], 0.1 ml buffer of displacing drug and 0.8 ml tissue suspension. Following incubation at 25 °C for 30 min, the assays were rapidly filtered under vacuum through Whatman GF/B filters with two 5-ml washes using 50 m*M* Tris-HCl buffer. Radioactivity was measured by liquid scintillation spectroscopy in 5 ml Aquasol (New England Nuclear; Boston, Mass) at 54% efficiency. Specific binding was defined using 1 μ*M* (+)butaclamol for ^{3}H-spiperone binding in caudate membranes, 1 μ*M* chlorpheniramine for ^{3}H-pyrilamine binding, and 1 μ*M* scopolamine for ^{3}H-QNB binding (both performed in cortical membranes). Generally, 75%–90% of total binding was specific for each radioligand. Radioligands were obtained from Dupont-New England Nuclear (Boston, Mass), and drugs were obtained from commercial sources.

Results

The interactions of cisplatin, 5-fluorouracil, doxorubicin, mitomycin, BCNU, cyclophosphamide, methotrexate, and thio-TEPA were assessed at three neurotransmitter receptor binding sites. The ability of each drug to compete for the specific binding at each neurotransmitter receptor site was analyzed using drug concentrations between 10^{-6} and 10^{-4} *M*. Each experiment was performed in triplicate and repeated three times. None of the eight agents significantly inhibited the specific binding of ^{3}H-spiperone, ^{3}H-pyril-

amine, or ^{3}H-QNB. Therefore, the eight chemotherapeutic agents did not interact with dopamine D_2, histamine H_1 or muscarinic cholinergic receptors at concentrations as high as 10^{-4} *M*.

Discussion

The major finding of the present study is that commonly used chemotherapeutic agents do not bind to neurotransmitter receptor binding sites that are believed to be involved in the pathogenesis of nausea and vomiting [2]. The ability of many antiemetics to block dopamine D_2, histamine H_1 and/or muscarinic cholinergic receptor sites strongly suggest that these receptors are involved in the mediation of nausea and vomiting [3]. The ability of chemotherapeutic agents to induce nausea and vomiting must therefore result from either a direct (primary) or an indirect (secondary) effect on central emetic pathways. Since the mechanism by which chemotherapeutic agents cause nausea and vomiting is unknown, direct activation of neurotransmitter receptors must be considered a potential action of these drugs. However, the inability of the eight agents to interact with dopamine D_2, histamine H_1 and muscarinic cholinergic receptors suggests that activation of central emetic pathways is a secondary rather than a primary effect of cancer chemotherapeutic agents.

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