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Advances in Brief

Stimulation of Malignant Growth in Rodents by Antidepressant Drugs at Clinically Relevant Doses[1]

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Abstract

Tricyclic antidepressants, such as amitriptyline (Elavil), and the nontricyclic agent, fluoxetine (Prozac), bind to growth-regulatory intracellular histamine receptors, associated with anti-estrogen binding sites in microsomes and nuclei. The prototype anti-estrogen binding site/intracellular histamine receptor ligand, *N,N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl, inhibits normal cell proliferation *in vitro* but stimulates tumor growth *in vivo*. Because of their structural similarity to *N,N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl, we carried out studies to determine whether amitriptyline and fluoxetine stimulate tumor growth and/or development in rodents at concentrations relevant to the treatment of human depression (equivalent human dose range, ~100–150 mg/day for amitriptyline and ~20–80 mg/day for fluoxetine). All experiments were performed blinded. In studies of growth stimulation of transplantable syngeneic tumors, groups of mice were inoculated s.c. with C-3 fibrosarcoma cells or given i.v. or s.c. injections of B16f10 melanoma cells, followed 24 h later by daily i.p. injections of saline, amitriptyline, or fluoxetine. Tumor latency (fibrosarcoma), aggregate tumor weight (s.c. injected melanoma), or time to death from pulmonary metastasis (i.v. injected melanoma) was determined; drug-induced stimulation of DNA synthesis in C-3 fibrosarcoma cells *in vitro* was correlated with tumor growth acceleration *in vivo*. In a mammary carcinogenesis model, the effects of chronic saline, amitriptyline, or fluoxetine administration on the rate and frequency of development of mammary tumors in rats fed dimethylbenzanthracene (DMBA) were compared. Eight of 20 amitriptyline- or fluoxetine-treated mice developed fibrosarcoma tumors by day 5, as compared to none of 20 saline controls ($P < 0.002$). Similarly, 20 of 21 DMBA-treated rats receiving the antidepressant drugs developed 33 mammary tumors by week 15 as compared to 5 tumors in 4 of 7 DMBA-treated rats receiving saline ($P < 0.001$). For both models, tumor latency decreased 30–40% and, in the DMBA model, tumor frequency increased >2-fold in the antidepressant-treated rats as compared to controls. Stimulation of fibrosarcoma growth *in vivo* correlated with a corresponding bell-shaped drug-induced increase in DNA synthesis *in vitro*. While the median time to death from pulmonary metastases did not differ among groups given i.v. injections of melanoma cells, a significant ($P < 0.01$) stimulation of growth of s.c. injected melanoma was observed in mice receiving the antidepressants. On the basis of these findings, we suggest that: (*a*) properly designed epidemiological studies be carried out to determine whether antidepressant drugs adversely affect the development or course of cancer in humans; and (*b*) preclinical drug screening procedures should include studies of tumor promotion, in addition to carcinogenesis.

Introduction

Episodes of serious depression affect up to 5% of the general population (1) and occur with a 3-fold higher frequency in patients with cancer (2). Tricyclic antidepressant drugs and newer nontricyclic agents such as fluoxetine (Prozac) cause rapid improvement in the symptoms of depression in a majority of patients, leading to a significant decrease in the length and/or severity of debilitation (3). Effective drug therapy for depression is especially important for patients with cancer, where quality of life often is already compromised from the side effects of surgery, radiation, and chemotherapy. Although classified as antagonists of serotonin uptake, the chemical structures of tricyclics and fluoxetine are similar to that of DPPE[3] (4), a potent ligand for AEBS which also bind tamoxifen (5).

We have shown an association of AEBS with novel intracellular H_{IC}, thus far identified in brain (6) and platelet membranes (7), liver microsomes (8), and nuclei (9, 10). Through binding H_{IC}, histamine functions as an intracellular second messenger in the mediation of human platelet aggregation (11, 12). Evidence is accumulating that intracellular histamine also promotes normal and malignant proliferation at H_{IC} (6, 8), possibly by modulating lipid/eicosanoid metabolism (10, 12). *In vitro*, at concentrations correlating with its antagonism of [^{3}H]histamine binding in rat liver microsomes and nuclei, DPPE inhibits DNA synthesis in normal lymphocytes stimulated to divide by concanavalin A (9) but increases DNA synthesis above an already high baseline in transformed lymphocytes or malignant cells (10). *In vivo*, DPPE (1–4 mg/kg) stimulates tumor growth in mice and rats; at a higher dose (32 mg/kg), it synergizes with phorbol 12-myristate 13-acetate to induce inflammation and epithelial hyperplasia in mouse epidermis (13). These changes are necessary for tumor promotion (14).

Many arylalkylamine derivatives structurally similar to DPPE, including H_1 antihistamines and phenothiazine-type neuroleptics, bind with varying potencies to AEBS/H_{IC} (15, 16). Therefore, we determined whether antidepressant agents also bind to H_{IC} and, at human-equivalent doses, mimic DPPE to stimulate tumor growth and development in rodents. We used amitriptyline and fluoxetine because both are widely prescribed for the treatment of depression.

Materials and Methods

Drugs

Amitriptyline·HCl was purchased from Sigma Chemical Co. (St. Louis, MO). Fluoxetine·HCl was obtained as commercially available 20-mg capsules (Prozac; Eli Lilly Co., Indianapolis, IN). Capsules were opened and the powder, containing 20 mg of active drug as the soluble HCl salt and 205 mg of insoluble cellulose-type filler per capsule, was added to sterile distilled water (2 ml/capsule). The resulting emulsion was poured into a 50-ml conical polypropylene tube (Corning Glassworks, Corning, NY) and centrifuged at 2800 × *g* for 20 min at room

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[3] The abbreviations used are: DPPE, *N,N*-diethyl-2-[4-(phenylmethyl)phenoxy] ethanamine HCl; AEBS, anti-estrogen binding sites; H_{IC}, intracellular histamine receptors; DMBA, dimethylbenzanthracene; Con A, concanavalin A; i.g., intragastric.

temperature. The supernatant, containing 10 mg/ml fluoxetine·HCl, was decanted off and stored at 4°C until used; the drug is said to be stable for at least 6 months in solution (insert provided by Lilly).

Binding Studies

To assess the potency of the agents for high affinity (nM) H_{1C} sites present in the nuclear fraction, porcine liver nuclei were prepared as described previously for rat liver nuclei (9). Fresh nuclear aliquots (protein concentration, 1–1.5 mg/ml) were incubated at room temperature in the dark for 60 min with 5 nmol [^{3}H]histamine in the presence or absence of increasing concentrations of cold histamine, amitriptyline, or fluoxetine. The reaction was terminated by centrifugation at 12,000 × *g* for 15 min at 4°C. Radioactivity was quantitated in a Beckman liquid scintillation counter and binding data were analyzed using the LIGAND program (17).

Mitogenesis Studies

To assess the *in vitro* potency of the agents to inhibit normal lymphocyte proliferation, fresh spleen cells (5×10^5) obtained from 5-week-old BALB/c mice (Charles River, St. Constant, Quebec, Canada) were suspended in RPMI 1640 containing 2% fetal calf serum (Grand Island Biological Co., Grand Island, NY), seeded into replicate NUNC microwell plates to which Con A (5 μg/ml; Sigma) was added and incubated in the presence or absence of increasing concentrations of amitriptyline or fluoxetine at 37°C in an atmosphere of 5% CO_2 and 95% air. At 43 h after the addition of Con A, 0.25 nmol [^{3}H]thymidine (6.7 Ci/mmol; ICN Radiochemicals, Montreal, Quebec, Canada) was added to each well. After an additional 5-h incubation, the cells were washed from the wells onto filters using an automated cell sorter. The filters were placed into vials containing scintillation fluid and radioactivity incorporated into DNA at 48 h was determined. To assess cytotoxicity as a basis for any observed antiproliferative effects, cell number (hemocytometry) and viability (trypan blue dye exclusion) were compared to values in controls treated with buffer alone and controls treated with Con A alone.

Tumor Models

C-3 Fibrosarcoma Model

***In Vivo* Study.** C-3 fibrosarcoma cells (derived from H-*ras*-transfected 10T½ fibroblasts) injected s.c. into the shaved gluteal tissue of C3H mice grow into a palpable tumor nodule (median appearance time, 7 days; all animals usually develop tumors within 10 days) (10). In two separate experiments, groups of 10 mice were given injections of 1×10^5 C-3 cells. Starting 24 h later, daily i.p. injections of saline (controls), amitriptyline (80 mg/m^2; Experiment 1), or fluoxetine (40 mg/m^2; Experiment 2) were administered. The cages were coded so that a second individual assessing the development of tumors was unaware of the treatment.

***In Vitro* Study.** To determine the effect of the antidepressant drugs on DNA synthesis, 5×10^3 C-3 cells were seeded into microwells (NUNC) containing 100 μl α-minimum essential medium supplemented with 10% fetal calf serum (Grand Island Biological Co.) and increasing concentrations (1×10^{-9}–1×10^{-5} M) of amitriptyline or fluoxetine. Replicates of 6 microwells were used for each concentration of drug; 12 control microwells contained cells alone in the absence of drug. The cells were incubated at 37°C in an atmosphere 5% CO_2-95% air. Nineteen h later, 0.25 nM [^{3}H]thymidine was added to each microwell. Following an additional 5-h incubation, the cells were washed from the wells onto filters using an automated cell sorter. The filters were placed in vials containing scintillation fluid and the radioactivity incorporated into DNA was determined.

B16f10 Melanoma Models

B16f10 melanoma cells, injected i.v. into the tail veins of C57Bl mice, cause death (median, 16–17 days) from multiple pulmonary metastases (10). When injected s.c., tumors grow locally within 7–10 days. Groups of 10 mice were given i.v. injections of 5×10^5 B16f10 cells, while groups of 5 were given s.c. injections into the gluteal region. Twenty-four h later, daily i.p. injections of saline (control), amitriptyline (30, 60, or 75 mg/m^2), or fluoxetine (12, 16, 20, or 40 mg/m^2) were administered. The cages were coded so that the person making the observations was not aware of the treatment. The median time to death from pulmonary metastases in the first case, or aggregate tumor wet weight at day 17 in the second case, was determined for the various treatment groups.

DMBA-induced Mammary Carcinoma

When administered p.o. to 150-g female Sprague-Dawley rats (Charles River), DMBA induces mammary tumors 8–16 weeks later (18). Rats were given DMBA p.o. (20 mg in 2 ml peanut oil) using a syringe connected to a hollow curved needle with a special blunt end for i.g. gavage. The rats were then divided randomly into four groups of 7–8 animals and given saline, amitriptyline (80 mg/m^2), or fluoxetine (16 or 40 mg/m^2) i.p. each Monday through Friday. This 5-day/week schedule was equivalent to an average daily dose of 57 mg/m^2 for amitriptyline and of 11.5 mg/m^2 or 28.5 mg/m^2 for fluoxetine. Once weekly for 15 weeks, each group was examined for tumors by individuals unaware of the treatment given. All tumors were measured in two dimensions. Any deaths from tumor or other causes were recorded. For humane reasons, once an entire group of rats developed tumors, all surviving rats in the group were killed by CO_2 asphyxiation.

Statistical Analysis

To test for significant differences among control and antidepressant-treated groups, the following statistical analyses were performed: (*a*) for difference in C-3 tumor latency, Fisher's exact test (yes or no for presence of tumor, day 5) was used; (*b*) for differences in B16f10 melanoma tumor wet weights (day 17), the Pearson correlation coefficients were calculated and linear slopes tested; and (*c*) for DMBA mammary carcinoma, the Kruskal-Wallis test compared the number of tumors per group at week 15.

Results

Correlation of Affinity for Nuclear H_{1C} with Potency to Inhibit DNA Synthesis in Con A-stimulated Normal Lymphocytes. Fluoxetine and amitriptyline competed for [^{3}H]histamine binding to a high affinity species of H_{1C} in porcine liver nuclei (Fig. 1*A*). The dissociation constant (K_d) for histamine was $3.4 \pm 3.4 \times 10^{-8}$ M (mean ± SEM). The inhibitory constants (K_i) for fluoxetine and amitriptyline were $4.6 \pm 6.5 \times 10^{-8}$ M and $1.0 \pm 0.8 \times 10^{-7}$ M, respectively. Rank order of potency for the agents to bind H_{1C} correlated with their inhibition of Con A-stimulated DNA synthesis in normal spleen cells (Fig. 1*B*); the 50% inhibitory concentration for fluoxetine was $7.5 \pm 2.5 \times 10^{-7}$ M, and that for amitriptyline was $2.5 \pm 0.5 \times 10^{-6}$ M.

Potentiation by Antidepressant Drug Treatment of C-3 Fibrosarcoma Growth. Saline-treated C3H mice given injections of C-3 fibrosarcoma cells began to develop palpable tumors at day 6 postinjection, whereas fluoxetine-treated animals began to develop tumors by day 3, and amitriptyline-treated animals began tumor development by day 4 postinjection. In two experiments combined, 8 of 20 animals receiving the antidepressants, but no animals receiving saline, developed tumors by day 5 (Fig. 2*A*), ($P < 0.002$; Fisher's exact test). By day 10, all animals including controls had tumors; however, the acceleration of tumor appearance was approximately 30% in the animals receiving amitriptyline or fluoxetine.

Correlation of C-3 Tumor Growth Stimulation *in Vivo* and Increased DNA Synthesis *in Vitro*. The observed *in vivo* acceleration of C-3 fibrosarcoma growth by 30% in animals receiving

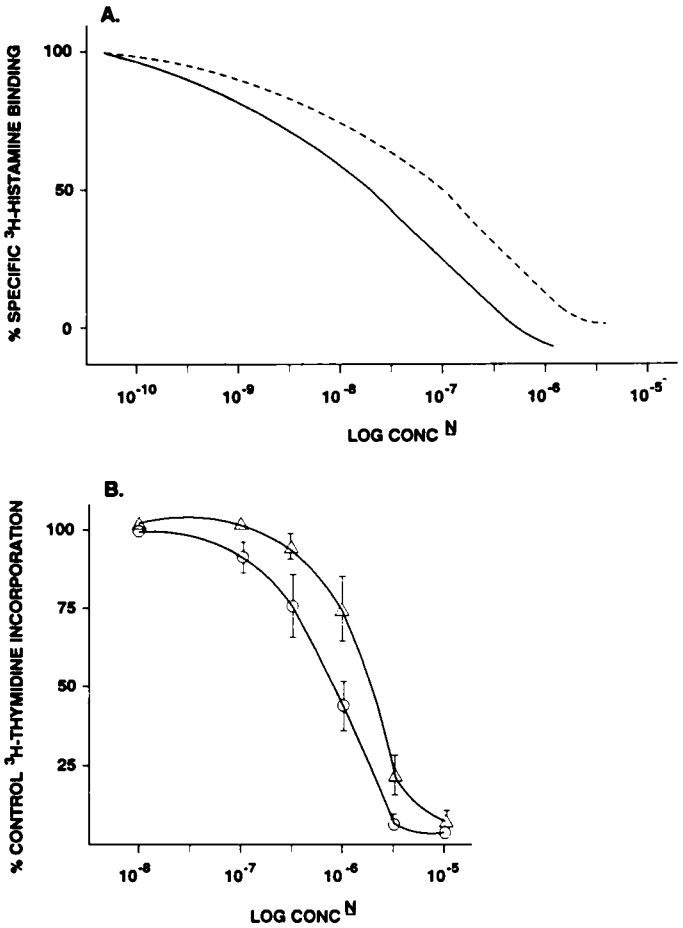

Fig. 1. *A*, potency of histamine (·····), fluoxetine (——), and amitriptyline (– – –) to inhibit [³H]histamine binding at a high affinity H_{1C} site in porcine liver nuclei (n = 3). *B*, potency of fluoxetine (○) and amitriptyline (△) to inhibit concanavalin A-stimulated DNA synthesis in normal mouse lymphocytes (n = 3; *bars*, SEM).

antidepressants correlated with a similar drug-induced increase in [³H]thymidine incorporation into DNA in C-3 cells *in vitro* (Fig. 2*B*). For both agents, a bell-shaped curve (optimal concentration, 1–5 × 10^{-8} M for fluoxetine and 1 × 10^{-7} M for amitriptyline) to increase thymidine incorporation into DNA by approximately 30–40% over baseline values was observed.

Potentiation by Antidepressants of s.c. B16f10 Melanoma Growth. No difference in survival among groups was observed when melanoma cells were injected i.v.; all survived for a median of 17 days. However, when the melanoma cells were injected s.c. (Fig. 3), the groups receiving amitriptyline or fluoxetine had significantly larger tumors than controls at day 17. [For amitriptyline, Pearson correlation coefficient (r) = 0.817; P = 0.0002. For fluoxetine, r = 0.632; P = 0.006.]

Potentiation of DMBA-induced Mammary Carcinogenesis. As compared to DMBA-treated rats receiving saline, those receiving the antidepressant agents had a significant acceleration of mammary tumor growth and development; stimulation by both low and high doses of fluoxetine was similar and was more potent than amitriptyline (Fig. 4). By week 15 after DMBA administration, the antidepressant-treated rats had developed an average of 11 tumors/group or 1.67 tumors/rat [8 tumors in 5 of 6 amitriptyline-treated rats; 12 tumors in 7 of 7 fluoxetine (11.5 mg/m²)-treated rats; 13 tumors in 8 of 8 fluoxetine (28.5 mg/m²)-treated rats], whereas the saline-treated group had developed 5 tumors in 4 of 7 rats or 0.71 tumor/rat (P < 0.001; Kruskal-Wallis test).

Overall, the latency to appearance of mammary tumors in the antidepressant-treated rats was decreased 30–40%, and the frequency of tumors increased up to 2.5-fold, as compared to saline controls. Moreover, both the mean area of tumors at first presentation (Fig. 5*A*), and aggregate tumor area at week 14 (Fig. 5*B*) were markedly higher in the antidepressant-treated rats than in saline controls; the largest tumors were found in

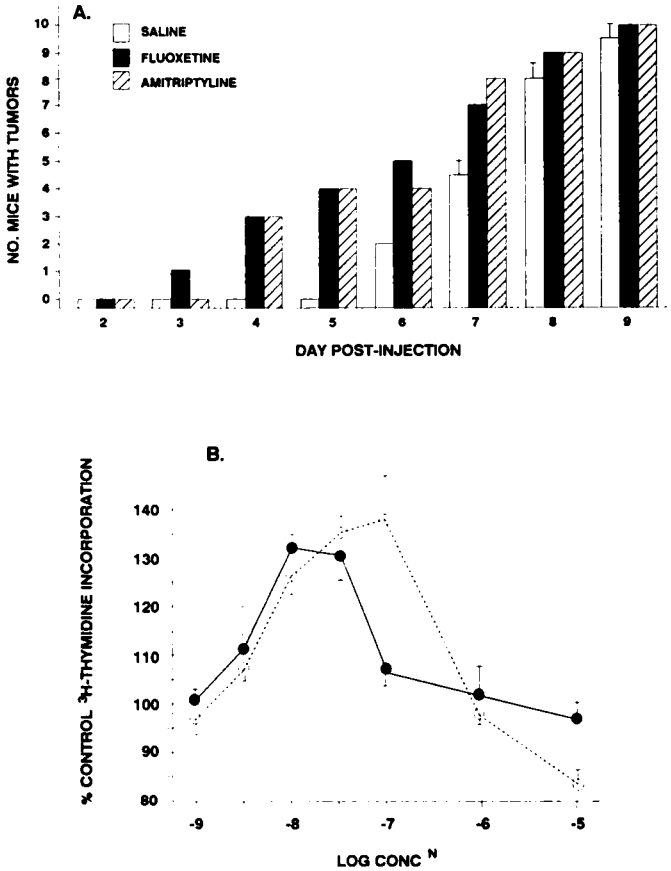

Fig. 2. *A*, time to appearance of a palpable tumor (C-3 fibrosarcoma) in mice given saline (n = 20), amitriptyline (80 mg/m²; n = 10), or fluoxetine (40 mg/m²; n = 10) once daily (*bars*, SD where differences for control values occurred in 2 separate experiments). *B*, stimulation by amitriptyline (○) and fluoxetine (●) of [³H]thymidine incorporation into DNA in C-3 fibrosarcoma cells (replicates of 6 or 12; N = 2; *bars*, SEM).

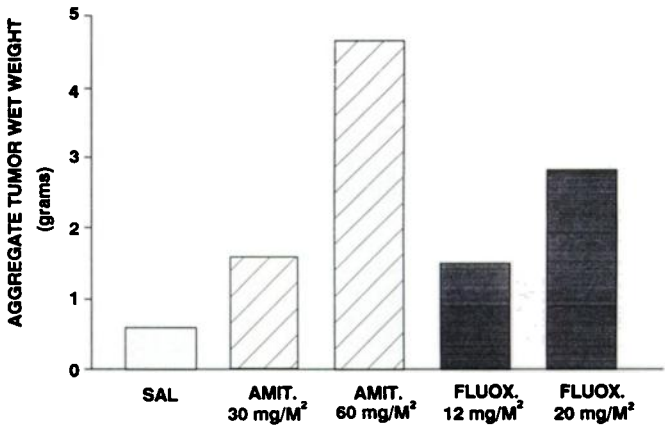

Fig. 3. Aggregate tumor wet weight at day 17 in groups of 5 C57Bl mice given s.c. injections of 1 × 10^5 B16f10 melanoma cells on day 1 followed by daily injections of saline (□) or amitriptyline (30 or 60 mg/m²) (▨) or saline or fluoxetine (12 or 20 mg/m²) (■).

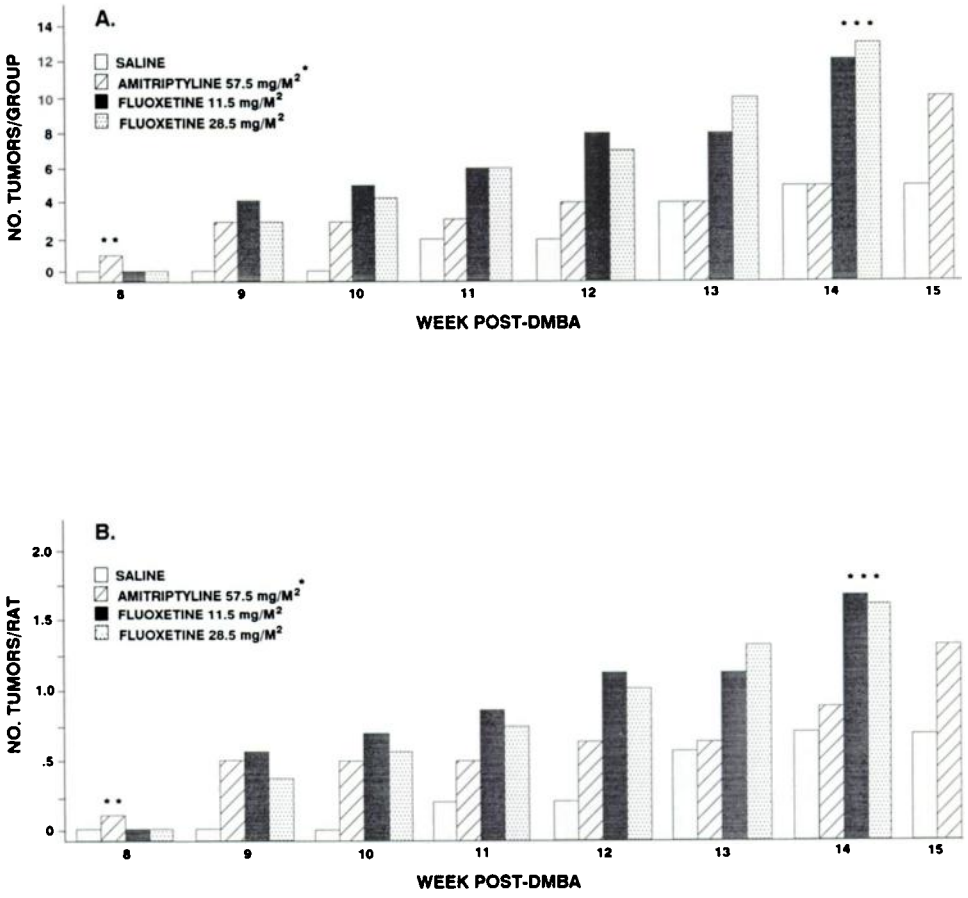

Fig. 4. Number of mammary tumors per group (*A*) and number of tumors per rat (*B*), as a function of time, in DMBA-treated rats receiving chronic administration of saline [n = 8], amitriptyline [57.5 mg/m^2; n = 8],* or fluoxetine [11.5 mg/m^2 (n = 7) or 28.5 mg/m^2 (n = 8)]. *, 2 amitriptyline-treated rats died (weeks 4 and 9) of apparent drug-related toxicity before developing tumors; **, developed a tumor at 2 weeks post-DMBA; ***, fluoxetine-treated rats were sacrificed at week 14 after all developed tumors).

animals receiving amitriptyline. Three animals (one at each dose of fluoxetine and one who received amitriptyline) died of rapid tumor progression between weeks 11 and 13; no DMBA-treated controls receiving saline died during the 15-week observation period.

In addition, 2 of the 8 DMBA-treated rats receiving amitriptyline died of apparent drug-related causes without developing tumors (1 at week 4; 1 at week 9). At autopsy, one of the rats had diffuse areas of old and new hemorrhage and erythrophagocytosis in the abdominal wall, lungs, and peritoneum, with evidence of rosetting of RBC around phagocytes, suggestive of an immune reaction. The second rat showed evidence of inflammation (pleuritis/epicarditis). No drug-associated toxicity was observed in DMBA-treated animals receiving saline or either dose of fluoxetine.

Discussion

The demonstration that amitriptyline and fluoxetine inhibit normal lymphocyte proliferation *in vitro* and promote tumor growth in 3 of 3 rodent models *in vivo* raises the question of whether they could have a similar effect in humans. For example, fluoxetine (20–40 mg/day) has been associated with 21 reported cases of reactivation of herpes simplex or zoster infection (19) suggesting that, even at the lowest range of prescribed doses, it can impair normal human immune function *in vivo*. Since we have shown that the stimulation of DNA synthesis in C-3 fibrosarcoma cells by amitriptyline and fluoxetine occurs at somewhat lower *in vitro* concentrations than does their inhibition of lymphocyte mitogenesis, the potential for these agents, likewise, to promote *in vivo* tumor growth in humans at clinically relevant doses must be assessed.

While many epidemiological studies have addressed a possible connection between human depression and cancer incidence, mortality or outcome (20–23), the results have been conflicting. However, the only study examining the use of neuroleptics (including antidepressants, tranquilizers, and hypnotics) antedating the diagnosis of cancer found a significantly higher incidence of metastases at presentation, or within 1 year of diagnosis, in those patients who reported taking such drugs in the preceding 12 months (24). In view of our findings, we suggest that new epidemiological studies be carried out to ask the following questions: (*a*) Do depressed patients on chronic antidepressant therapy run a significantly higher risk of developing cancer than those not on antidepressants? (*b*) Is a putative increased risk of developing cancer from taking antidepressant drugs dependent on concomitant exposure to a tumor initiator, *e.g.*, cigarette smoke? (*c*) Do antidepressant drugs accelerate the clinical course if cancer is already present?

Finally, our studies also raise an equally important question concerning the adequacy of using tests only for carcinogenicity in preclinical toxicology studies. Information provided on fluoxetine states that no carcinogenesis was observed in mice receiving 5–9 times the human-equivalent dose of drug for 24 months (25); moreover, there was no evidence of mutagenicity in the Ames test or in assays for induction of double-stranded DNA breaks (25). However, while undoubtedly of predictive value, standard tests for mutagenesis/carcinogenesis appear to miss the potential of drugs to act as tumor promoters when cancer is already present, or to accelerate the development of malignancy in the presence of chemical or viral initiators.

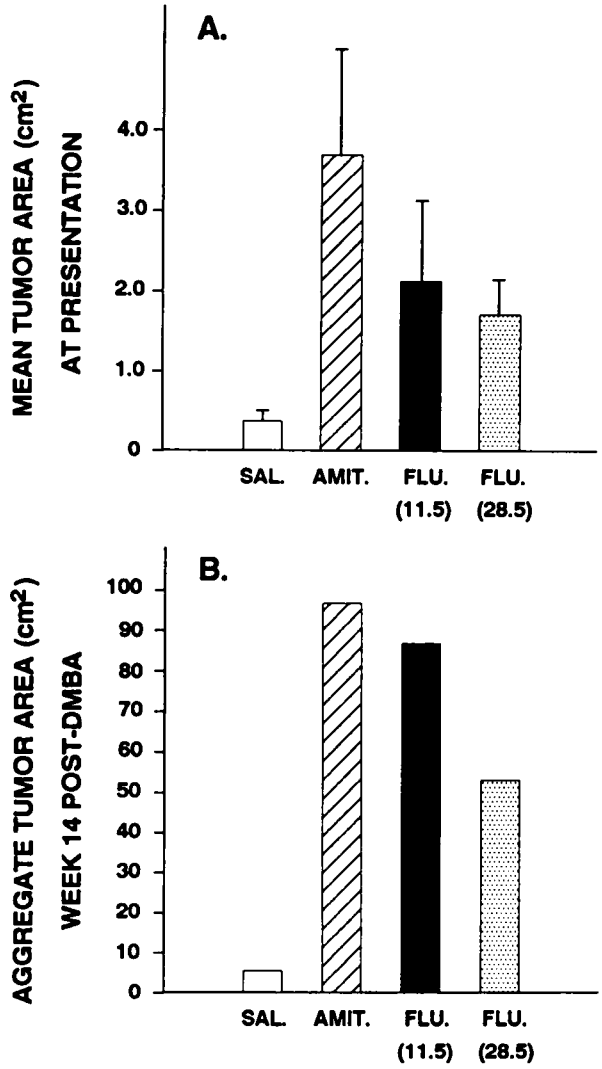

Fig. 5. Mean area (*bars*, SE) of tumors at first detection (*A*) and aggregate tumor area (week 14) (*B*) in DMBA-treated rats receiving chronic administration of saline, amitriptyline (57.5 mg/m^2), or fluoxetine (11.5 or 28.5 mg/m^2). The values include aggregate tumor areas in 3 rats at the time of death prior to week 14 (1 amitriptyline; 1 at each dose of fluoxetine).

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Addendum

Recently, tamoxifen was reported to accelerate the growth of hormonally independent mammary carcinoma induced by DMBA in rats (26). Although the mechanism was not identified with certainty, an action at anti-estrogen binding sites was considered. Our observations with antidepressant drugs are consistent with this postulate, since, like tamoxifen, both amitriptyline and fluoxetine bind AEBS/H_{1C} and accelerate DMBA-induced mammary tumor growth.

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