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Influence of N,N-Diethyl-2-[4-(Phenylmethyl) Phenoxy]Ethanamine (DPPE) on the Proliferation of Selected Cell Lines *in vitro**

Wpływ N,N-dietylo-2-[4-(fenylometylo)fenoksy]etanaminy (DPPE) na proliferację wybranych linii komórkowych *in vitro*

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Abstract

Background. Little is known of the effects of N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine (DPPE) on cell proliferation. Some studies indicate that DPPE inhibits cell proliferation and differentiation, especially under *in vitro* conditions, but the *in vivo* effect is not so clear. It stimulated the growth of chemically induced breast cancer in rat, for example, but inhibited the proliferation of human breast cancer cells *in vitro*.
Objectives. The aim of this study was to evaluate the effect of DPPE on the proliferation of neoplastic and normal cell lines *in vitro*.
Material and Methods. The study was carried out on four cell lines: human melanoma (BM), human breast cancer (MCF-7), human gastric cancer (EPG-85-257), and mouse normal fibroblasts (3T3-Balb). They were incubated under standard conditions in medium containing 10% fetal calf serum and a solution of L-glutamine and antibiotics. DPPE was used at concentrations of 400, 40, 4, and 0.4 μg/ml. A cell culture of 2×10^4 cells/ml density was established and 72 hours later the cells were counted, thus providing a preliminary control value. After changing the medium and supplementation with DPPE, the cells were incubated for another 72 hours and counted again. The final control (in the case where DPPE was not added) and final results (in the cases where DPPE was added) were established. The test value and test index were calculated from special formulae.
Results. Human melanoma and mice normal fibroblasts were very sensitive to DPPE in the two higher concentrations (400 and 40 μg/ml); their proliferation was strongly inhibited by DPPE. Human breast cancer and human gastric cancer were slightly sensitive to DPPE in the two higher concentrations; their proliferation was slightly inhibited by DPPE. At a lower concentration (4 μg/ml), only the human melanoma cells were slightly sensitive to DPPE; in this case, the proliferation of human melanoma cells was also inhibited by DPPE, but not as strongly as in the case of the two higher concentrations. Other cell lines were not sensitive to DPPE in the two lower concentrations (4 and 0.4 μg/ml) and proliferation was not inhibited.
Conclusions. Monotherapy of cancer with DPPE is rather not possible due to, among other reasons, its toxicity to normal cells. However, adjuvant therapy with DPPE cannot be excluded. Further studies are necessary (**Adv Clin Exp Med 2006, 15, 6, 989–994**).

Key words: DPPE, neoplastic cells, proliferation, *in vitro* studies.

Streszczenie

Wprowadzenie. Niewiele wiadomo o wpływie N,N-dietylo-2-[4-(fenylometylo)fenoksy]etanaminy (DPPE) na proliferację komórek. Niektóre badania wskazują, że DPPE hamuje proliferację i różnicowanie się komórek, zwłaszcza *in vitro*, działanie DPPE *in vivo* nie jest jednak tak jednoznaczne. DPPE pobudza np. wzrost wyindukowanego chemicznie raka sutka u szczurów, chociaż hamuje proliferację komórek raka sutka *in vitro*.
Cel pracy. Określenie wpływu DPPE na proliferację wybranych linii komórek prawidłowych i nowotworowych w warunkach hodowli *in vitro*.

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Materiał i metody. Badanie zostało przeprowadzone na czterech liniach komórkowych: ludzkiego czerniaka (BM), ludzkiego raka sutka (MCF-7), ludzkiego raka żołądka (EPG-85-257) oraz mysich prawidłowych fibroblastach (3T3-Balb). Wszystkie linie komórkowe były inkubowane w standardowych warunkach, podłoże hodowlane zawierało dodatek 10% płodowej surowicy cielęcej oraz roztwór L-glutaminy i antybiotyków. W doświadczeniu zastosowano następujące stężenia DPPE: 400, 40, 4 i 0,4 μg/ml. Komórki były liczone po 72 godz. od założenia hodowli o gęstości 2×10^4 kom/ml, co było kontrolą wstępną. Po wymianie medium hodowlanego i dodaniu badanego związku w odpowiednich stężeniach komórki były inkubowane przez kolejne 72 godz., a następnie liczone, co było kontrolą ostateczną (gdy nie dodano DPPE) lub wynikiem ostatecznym (gdy dodano DPPE do hodowli). Wartość testu oraz indeks testu wyliczono na podstawie odpowiednich wzorów.
Wyniki. Ludzki czerniak i rak sutka były wrażliwe na działanie DPPE zastosowane w dwóch większych stężeniach (400 i 40 μg/ml). Proliferacja komórek tych dwóch linii została w znacznym stopniu zahamowana przez DPPE. Ludzki rak sutka oraz rak żołądka były mało wrażliwe na działanie DPPE w tych samych stężeniach. Proliferacja komórek tych dwóch linii była hamowana słabiej niż w przypadku poprzednich dwóch linii komórkowych. Gdy DPPE zastosowano w mniejszym stężeniu (4 μg/ml), tylko linia ludzkiego czerniaka była mało wrażliwa. Proliferacja komórek czerniaka ludzkiego była hamowana słabiej niż w przypadku większych stężeń DPPE. Pozostałe linie komórkowe nie były wrażliwe na badany związek zastosowany w dwóch mniejszych stężeniach (4 oraz 0,4 μg/ml), ich proliferacja nie była hamowana przez badany związek.
Wnioski. Terapia chorób nowotworowych samym DPPE wydaje się raczej mało prawdopodobna, chociażby z powodu jego toksyczności wobec komórek prawidłowych. Nie można jednak wykluczyć zastosowania tego związku w terapii wspomagającej klasyczną chemioterapię (**Adv Clin Exp Med 2006, 15, 6, 989–994**).

Słowa kluczowe: DPPE, komórki nowotworowe, proliferacja, badania *in vitro.*

N,N-diethyl-2-[4-(phenylmethyl)phenoxy] ethanamine (DPPE), a derivative of tamoxifen, was synthesized by Brandes et al. in the early 1980s. Like tamoxifen, DPPE binds with high affinity to the anti-estrogen binding site [1, 2]. DPPE is also considered to be an intracellular histamine binding inhibitor [3], inhibiting histamine binding to some isoenzymes of cytochrome P-450 [4]. The family of P-450 isoenzymes contributes to the regulation of cell growth by modulating the levels of steroids and other lipid messengers for cytoplasmic and nuclear processes, including gene expression [5]. The P-450 isoenzymes also metabolize several classes of antineoplastic agents. It is suggested that DPPE inhibits the p-glycoprotein pump, the overexpression of which is implicated in drug resistance [6]. Some authors consider the intracellular histamine binding site as a subclass of the histamine receptors $H_{(ic)}$ [7–10].

Little is known of the effects of DPPE on cell proliferation. Some studies indicate that DPPE (like tamoxifen) inhibits cell proliferation and differentiation, especially under *in vitro* conditions, but the *in vivo* effect is not so clear [2, 11–13]. DPPE promotes the growth of transformed or malignant cells with a bell-shaped dose-dependent curve. At low doses, DPPE even accelerates tumor growth in rodents. As the dose of DPPE increases, growth promotion decreases, and at higher *in vitro* concentrations, DPPE is antiproliferative/cytotoxic to different human and animal cell lines. DPPE stimulated, for example, the growth of chemically induced breast cancer in rats and of leukemia in mice [14], although it inhibited the *in vitro* proliferation of human breast cancer cells [11]. DPPE also significantly potentiates the cytotoxicity of antineoplastic drugs to cancer cells [12, 15]. However, an exact preclinical mechanism of DPPE action that would explain such an effect is unknown.

The aim of this study was to evaluate the effect of DPPE on the proliferation of neoplastic and normal cell lines *in vitro*.

Material and Methods

Cell Cultures and Chemicals

The study was performed on the following normal and neoplastic cell lines: human melanoma (BM), human gastric cancer (EPG-87-257), human breast cancer (MCF-7), and mouse normal fibroblasts (3T3-Balb). All cell lines were cultured in the Laboratory of Cell Culture of the Department of Histology and Embryology, Silesian Piasts University of Medicine in Wrocław.

In this study, the following chemicals were used: N,N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine fumarate (DPPE fumarate, Tocris, UK), MEM (Minimal Essential Medium of Eagle, BioWhittaker, Belgium), 10% FCS (Fetal Calf Serum. BioWhittaker, Belgium), L-glutamine, penicillin, and streptomycin solution (2 mM of L-glutamine, 100 IU of penicillin per ml, and 100 μg of streptomycin per ml; Sigma, USA), Trypsin and EDTA solution (25 mg of trypsin and 2 mg of EDTA per ml, Sigma, USA), and *Aqua pro iniectione* (Polpharma S.A., Poland).

Experimental Setup

Tests on the cells cultured *in vitro* determined their proliferation and further development in the presence of the studied compound [16]. For each studied cell line, the experiment involved 1) establishing the culture, 2) preparing a suspension of cells of 2×10^4/ml density, 3) counting the cells after 72 hours (preliminary control: C_p), 4) exchanging the medium (without or with addition of the studied preparation at various concentrations) and culturing for another 72 hours, and 5) counting the cells (final results: C_x or final control: C_f).

All the cells grew in monolayers adhering to the bottom of the culture containers filled with MEM supplemented with 10% FCS and the solution of L-glutamine, penicillin, and streptomycin. The cultures were maintained at 37°C in 5% CO_2. A solution of trypsin and EDTA was used to recover cells from the culture containers for the test, which was performed in MEM.

Cells at the stage of active growth were removed from the bottle, after which they were counted and a suspension of 2×10^4/ml density was prepared. The main experiment was performed in 24-well culture plates (NUNCLON, Denmark). Each well was charged with 1 ml of the suspension. Three days later the fluid was replaced with fresh culture medium with DPPE in the studied concentrations or without DPPE. DPPE was dissolved in distilled water (*Aqua pro iniectione*) and subsequently microfiltered. The concentrations of DPPE used in the tests were 400 μg/ml, 40 μg/ml, 4 μg/ml, and 0.4 μg/ml. At the same time, the cells were counted in order to establish the growth of cells from the time of setting up the culture until the day of starting the test proper. This provided the preliminary control (C_p) value. All cell lines were incubated for a subsequent 72 hours under standard conditions, and the cells were counted again. The obtained result represented the final control (C_f) value when DPPE had not been added or a final result (C_x) if the studied preparation had been added to the culture medium.

The test value (TV) and test index (TI) were calculated according to the formulae:

$$TV = \frac{C_x - C_p}{C_f - C_p} \times 100\%$$

$$TI = TV \times \frac{C_p}{C_x}$$

A test index (TI) lower than –80% signified that the cells were sensitive to the studied compound and proliferation of the tested cells was strongly inhibited by the studied compound. With values ranging between –40 and –80%, the cells were regarded as slightly sensitive to the studied compound (proliferation of the tested cells was also inhibited, but to a lesser extent than in the previous case), while with values exceeding –40% it was assumed that the cells were not sensitive to the studied substance and proliferation of the tested cells was not inhibited by the studied compound. It should be pointed out that these values concern cytostatic drugs which are considered standard preparations with very strong activity [16].

Results

The human melanoma cells and mouse normal fibroblasts were sensitive to DPPE in the two higher concentrations (400 and 40 μg/ml); proliferation of these cell line was strongly inhibited by DPPE. The human breast cancer and human gastric cancer cells were slightly sensitive to DPPE at these concentrations; proliferation of these two cell lines was slightly inhibited by DPPE. When DPPE was tested in the lower concentrations (4 and 0.4 μg/ml), only the human melanoma cells were slightly sensitive to the studied compound at a 4 μg/ml concentration. In this case the proliferation was also inhibited by DPPE, but not so strongly as in the case of the two higher concentrations of DPPE. Other cell lines proved insensitive to the studied substance in the lower concentrations, and their proliferation was not inhibited by DPPE. The exact test values and test indexes for each tested cell line and each DPPE concentration are presented in Table 1.

Discussion

The influence of DPPE on cell proliferation is very unclear. It inhibited, for example, the proliferation of human peripheral progenitor cells, decreasing the number of erythroid and granulocyte macrophage colonies [13]. However, the DPPE concentrations used in that test were very high (over 400 μg/ml). It was shown that DPPE also inhibited the proliferation of human breast cancer MCF-7 [11]. Contrary to that study, performed by Brandes et al., the present experiment showed DPPE slightly inhibiting (according to the criteria for cytostatic drugs) the proliferation of MCF-7 human breast cancer cells. However, the duration of the tests was different in these two studies: seven days of incubation with DPPE in the previous study vs. three days in the present experiment. It cannot be excluded that a more pronounced influence of DPPE on the proliferation of

Table 1. Test values (TV) and test indexes (TI) for each tested cell line and each DPPE concentration

Tabela 1. Wartości testu (WT) oraz indeksy testu (IT) dla każdej badanej linii komórkowej i każdego zastosowanego stężenia DPPE

	Cell line (Linia komórkowa)							
	3T3-Balb – mouse normal fibroblasts (mysie prawidłowe fibroblasty)		BM – human melanoma (czerniak ludzki)		MCF-7 – human breast cancer (ludzki rak sutka)		EPG-85-257 – human gastric cancer (ludzki rak żołądka)	
DPPE concentration (Stężenie DPPE) µg/ml	TV WT %	TI IT %	TV WT %	TI IT %	TV WT %	TI IT %	TV WT %	TI IT %
400	–188.1	–131.7	–650.0	–585.0	–124.5	–74.7	–87.8	–43.9
40	–168.7	–118.1	–600.0	–540.0	–118.2	–70.9	–81.1	–40.6
4	–49.3	–34.5	–50.0	–45.0	–21.4	–12.8	18.5	9.3
0.4	–29.9	–20.9	0.0	0.0	63.6	38.2	78.7	39.4

MCF-7 cell line could be exerted with longer incubation in the present experiment.

In this study, DPPE strongly inhibited (to an extent comparable to cytostatic agents) the proliferation of human melanoma (BM) cells and murine normal fibroblasts (3T3-Balb) in the two higher concentrations (400 and 40 µg/ml). However, the pronounced damage in normal cells (such as fibroblasts) evoked by higher concentrations of DPPE present a rather unfavorable feature. It could be evidence for a narrow therapeutic index of the tested substance. In clinical trials, DPPE was administered to humans in doses of 4–6 mg/kg (together with cytostatic drugs) and plasma concentrations ranged between 0.4 and 2 µg/ml [17]. In the present study, DPPE at a concentration similar to that obtained in human blood (4 µg/ml) slightly decreased the proliferation of human melanoma cells without inhibiting fibroblast proliferation. When the lowest concentration was used (0.4 µg/ml), the test index for this cell line was 0, which indicated no influence of DPPE on melanoma cell proliferation. In the study by Falus et al. [18], the different inhibitory effects on the proliferation of melanoma cell lines (by 14.5–21%) by DPPE in a concentration of 10^{-6} M were observed (e.g. EP, HT, MI/15, WM35, WM938). In the present study, similar inhibition (by 17%) of melanoma cell proliferation in a corresponding concentration (0.4 µg/ml) was observed (data not shown).

The present results indicate that DPPE only slightly inhibits the proliferation of the EPG-85-257 human gastric carcinoma cell line. This effect was observed only at the two higher concentrations of DPPE (400 and 40 µg/ml). What is more, in the lowest concentration of DPPE used in the experiment, DPPE even slightly promoted the proliferation of this cell line (TI = 39.4%). A similar tendency was observed in the case of the cell line of human breast cancer (MCF-7) tested in this study. The test index for DPPE concentration of 0.4 µg/ml was 38.2%. Some *in vivo* studies suggest that DPPE at low doses even accelerates tumor growth in rodents. It was shown that DPPE stimulated the growth of chemically induced mammary cancer in rats and leukemia in mice and synergizes with phorbol-12-myristate-13-acetate to induce inflammation and mitotic activity in mice [14, 19]. A similar tendency to promote cell proliferation could be observed in the present *in vitro* study. However, it was demonstrated that DPPE reduced tumor size in human colorectal cancer in a subrenal capsule assay [20]. Also, the combination of DPPE and cimetidine inhibited the proliferation of human melanoma cells (HT-168) *in vitro*, and this combination also increased the survival of human melanoma-grafted mice. However, in that study, DPPE administered alone even (non-significantly) stimulated tumor growth [21, 22]. The mechanism of such dual action of DPPE on cell proliferation is not well understood and explained. It is suggested that the influence of DPPE on cell proliferation may depend on both the concentration and the model used in the experiment (*in vitro* or *in vivo*).

In the mid 1980s, new evidence was presented that the intracellular anti-estrogen binding site could be a growth-promoting histamine receptor [23]. N,N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine (DPPE), which selectively binds the anti-estrogen binding site, may be also an intracellular histamine antagonist [3]. The presence of the new intracellular histamine receptor $H_{(ic)}$, involved in cell proliferation, was suggested [8]. Intracellular histamine was implicated to mediate, for example, mitogenesis in normal mouse spleen cells stimulated by concanavalin A. Either DPPE

or fluoromethylhistidine (FMH) blocked this action of histamine [9]. The different activity of DPPE upon cell proliferation could be connected with the different effects of this substance on histamine binding to cytochrome P-450 isoenzymes. It has inhibited, for example, histamine binding to CYP2D6 and CYP1A1 isoenzymes, failing to affect binding with CYP2B6, but even increasing histamine binding to CYP3A4 isoenzyme [4]. The effect of DPPE on cytochrome P-450 isoenzyme activity has just been used in clinical trials. DPPE potentiates the cytotoxicity of antineoplastic drugs, but protects normal cells because of the different activity of cytochrome P-450 enzymes (especially CYP3A4) in cancerous and normal cells [4, 17, 24]. Some experimental and clinical trials evaluating the effectiveness of concomitant therapy with DPPE and classical anticancer drugs, e.g. doxorubicin or cisplatin, have already been undertaken [2, 6, 15, 24]. DPPE also inhibits concanavalin A-induced histamine release from mast cells [25]. Histamine is postulated as a modulator of cell proliferation, growth, and differentiation, especially in different melanoma cell lines [26].

In the light of the present study, the therapy of cancer diseases with DPPE as a cytostatic drug remains a rather distant possibility, due, for example, to its toxicity to normal cells in the concentrations in which DPPE exerted strong cytotoxic action. However, the potential for adjuvant therapy with DPPE (e.g. with classical anticancer drugs) cannot be excluded, especially in the treatment of melanoma, because DPPE showed slight activity against BM melanoma cell line also at a lower concentration (4 mg/ml), which could be obtained in the human blood. Such a clinical trial was conducted in the treatment of, for example, breast cancer and ovarian cancer and their results are promising [2, 6]. Further detailed studies are necessary, especially on the combined therapy.

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