EFFECT OF OLIGOELEMENTS AND PHOSPHOLIPASE A2 ON TUMOR CELL GROWTH AND INDUCTION OF APOPTOSIS. IN VITRO STUDIES.

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Aim: In the present work we investigated the direct action of A2 phospholipase and the oligoelements Zn, Sr and Mn (O-PAs) on in vitro cell proliferation and on the induction of apoptosis in malignant cells. We studied the effect of these compounds on cell proliferation and on the induction of apoptosis in malignant cells.

Methods: Cancerous suspensions from chemically induced mammary carcinomas were cultured under soft agar and the effect of different doses of O-PAs was studied by evaluating colony formation. In order to evaluate, cell lines derived from diverse human neoplasms and normal, non-transformed epithelial cells, were challenged with O-PAs at concentrations from 10^{-2} to 10^{-6} μg/ml and proliferation was evaluated by different methods. Induction of apoptosis was investigated in experimental carcinomas developed in control animals and in tumors from rats treated with O-PAs. The proportion of apoptotic cells was evaluated by employing immunochemical methods.

Results: Data obtained in vitro with all neoplastic cells indicated that O-PA produced a dose-dependent inhibition on cell proliferation. The maximal inhibitory response observed was 50% (p < 0.01 versus control cell cultures) with slight differences among the different cell lines. When normal cells were tested, although not significant, an increase in cell proliferation was observed with lower O-PA doses. In the experimental carcinomas, studies of apoptosis indicated a significant higher number of apoptotic cells in all the tumors from rats pre-treated with O-PAs. On the contrary, in tumors from control rats, only a low number of apoptotic cells were observed and the increase was in the tumors.

Conclusions: These results clearly demonstrate that O-PAs treatment exerts a direct action on tumor cells. The final response of this effect as a significant inhibition on cell proliferation may be consequence of an induction of apoptosis and/or cell differentiation. This effect proved to be a differential action on transformed cells, not observed in normal cell lines.

ANTITUMORAL ACTIVITY OF A NEW SERIES OF 5-A-DIHYDROERENZO(AC)CARBAZOLES


Aim: To synthesize drugs with antitumoral activity. The overlapping of three-dimensional structures of 2,4-dihydropyrano[3,2-α]carbazoles (DHDCs) derivatives over the structure of 2-hydroxy-4-triazolylacetone (4-CHTAM), a possible aroma of the computational program, shows a reasonable structural and spatial resemblance. This finding raised the possibility of their possible anti-tumoral activity, similar to that of tamoxifen (TAM).

Methods: A number of DHDCs (9 in all) with an acyl chain and a second basic nitrogen in substitution, were synthesized in our laboratory and tested against anti-tumoral activity tested by means of 1) competitive radioligand assay to determine relative drug binding affinity for the estrogen receptor of post-partum rabbit uterus (RBA); 2) in vivo studies, giving the synthetic drugs subcutaneously (1 mg/kg/day) in Sprague-Dawley rats with Nmu-induced mammary tumors; and 3) in vitro tumor cell proliferation experiments employing the soft agar clonogenic technique.

Results: 1) RBA for the estrogen receptor were similar to that of TAM (0.4 ± 0.02) for all compounds. 2) Only three synthetic structures showed important anti-tumoral activity and induced tumor regression similar to TAM (12, 44, 47 vs 48%, respectively, p < 0.05, and 3) three these compounds also produced in vitro inhibitory effect on cell proliferation (p < 0.05 versus control). Tumor growth rate of regressed and non-regressed tumors was similar to that of TAM. Survival of these treated rats was similar to that of mice treated with TAM.

Conclusion: Though all the compounds of the series of synthesized DHDCs showed affinity for the estrogen receptor similar to TAM, the results in in vivo and in vitro experiments confirmed the crucial role of hydroxyl groups in the molecules and of the inverse distance between them, similar to that of estradiol, as well as the necessity presence of the amine chain on the aromatic N atom. Further investigations would be important in a view of a promising future for mammary tumor therapy of the three DHDCs derivatives with antitumoral activity.

TRENDS IN SMOKING PREVALENCE AND LUNG CANCER MORTALITY IN POLAND

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Aim: To evaluate trends and patterns in lung cancer mortality in Poland and to explain possible association with changes in tobacco use indicators.

Methods: Analyses of annual standardized and age-specific lung cancer mortality rates by sex and of smoking prevalence rates by sex for specific age groups from the nation-wide randomized surveys carried out in adult population.

Results: Lung cancer is still leading cancer in male population in Poland and is the second frequent cancer site in women. An overall lung cancer mortality in males in Poland was increasing from the beginning of 1960s to the end of 1980s. In 1990 no further increase was observed. Some decrease of cancer mortality has been recorded in young adults (aged 20-44) since the beginning of 1980s. In the middle-aged males (45-64), increase of mortality has been stopped by end of 1990s. Lung cancer mortality rates for older males (65 and over) have grown in the entire time period. Positive changes in lung cancer mortality have not been noted in female population. Trends in lung cancer mortality reflect changes in tobacco smoking in Poland. The following changes in smoking behaviours among men are considered to explain the halting of increase in lung cancer mortality in young and middle-aged men: (1) almost two-fold increase in percentage of never smokers, (2) substantial increase in ex-smoking rates, (3) considerable decrease in daily smoking rates especially among young age groups. Although these no significant changes in smoking attitudes in all women (besides increase in ex-smoking-rates), we have observed decrease of daily smoking in young women. It is linked upon lung cancer mortality in this population in coming years.

Conclusion: Comparison with other CEE countries shows that implementation of the national tobacco control programs and policy can be effective method to stop the epidemic of tobacco-related cancer in CEE in coming decade.
161 ACTION OF OILGEOIDES AND PHOSPHOLIPASE A2 ON THE VENOM TOXICITY TO TREATMENT WITH HIGH CYSTATIN DOSES.

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AIM: To evaluate in vivo and in vitro tolerated treatment with phospholipase A2 and oilgoides drugs used for human breast cancer combined with different doses of oilgoides.

Methods: In vivo experiments snake Squalence-Dwyer rats were employed. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) injection was injected in rats treated with or daily admission of 0.4 mmol kg^-1 /day saline or CMF. Range of CMF doses were used in different batches covered from 1 to 10-fold the dose was evaluated in human patients with breast cancer. CMF injection, different cell lines derived from human breast cancer xenograft and breast cancer xenograft were employed. Cells were cultured in appropriate supplement medium and grown in suspension or monolayers in accord with their characteristics. 5-fluorouracil (5-FU) was tested in different doses.

Result: In vivo results indicate a significantly higher survival in treated rats versus control. Even with very high doses of CMF (14 to 18-fold dose used in humans), data indicated a significant difference versus control. CMF for the 5-FU treated group. CMF injection showed similar effects on cell proliferation rates similar to 133 U/M. In vitro experiments showed similar effects on cell proliferation rates similar to 133 U/M. This finding was confirmed by 5-FU injection that showed the same pattern of growth control, while at 100 µM a significant number of viable cells remained after 5-FU treatment.

Conclusions: In vivo results demonstrate the protective immunomodulatory action of CMF, but rate received oils in combination with cyclophosphamide drugs with oils have the potential to be considered in cancer treatment.

162 ANTIMICROBIAL ACTIVITY OF A NEW SERIES OF 5,6-DIHYDROXYBENZOIC ACID DERIVATIVES.

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AIM: To synthesize drugs with antimicrobial activity. The screening of three-dimensional structures of 2,3-dihydroxybenzoic acid (DHB) derivatives over the structure of 4-hydroxybenzoic acid by MCL CHEN et al, has been shown to be effective. The structure-activity relationship between the compounds and their antimicrobial activity was determined by means of 1) competitive radioligand assays to determine drug binding affinity for the estrogen receptor of post-menopause rabbit stroma (RBA), 2) in vivo studies, giving the synthetic drugs subcutaneously (1 mg/kg) to Sprague-Dawley rats with NMU-induced mammary tumors; and 3) in vivo tumor cell proliferation experiments employing the soft agar cloning technique.

Results: 1) RBA for the estrogen receptor was similar to that of TAM (0.54 ± 0.03) for all compounds; 2) only three synthetic structures showed important antimicrobial activity, and induced tumor regression similar to TAM (22, 44, 42 versus 40%, respectively, p NS); and 3) these compounds also produced in vivo inhibition effect on cell proliferation (p < 0.05 versus controls). Tumor growth rate of regressed and non-regressed tumors was similar to that of TAM. Survival of these treated rats was similar to that of TAM. Aphetamine studies demonstrated intramuscular necrosis and absence of hepatic and renal injury or other toxic effects.

Conclusion: Though all the compounds of the series of synthesized DHB were shown to have activity similar to TAM, the results of its in vivo and in vitro experiments confirm the crucial role of hydroxy groups in the molecule and of the intramolecular distance between them, similar to that of estradiol, as well as the necessity presence of 3-keto acids in the aromatic N atom. Further investigations would be important in view of a promising future for mammary tumor therapy of the three DHB derivatives with antimicrobial activity.