mediated by dynamin and dependent on calcineurin-induced dephosphorylation, activation of PKC, inhibition of synaptojanin and formation of PtdIns(4,5)P_2. The effect of $InsP_6$ on the L-type Ca^{2+} channel is mediated, at least in part, by inhibition of serine/threonine protein phosphatase activity. Our studies in neuronal cells have confirmed that the effect of $InsP_6$ specifically relates to L-type Ca^{2+} channels and have also introduced the additional observation that $InsP_6$ can activate adenylate cyclase, a key player in β-cell stimulus-secretion coupling. Moreover, our studies in beta cells demonstrate that a small but consistent transient elevation in $InsP_6$ concentration follows glucose stimulation and that the temporal changes in $InsP_6$ correlate well with the initial rise in $[Ca^{2+}]_i$ mediated by the channels. The small changes in $InsP_6$ concentration suggest the existence of a small, metabolically active but physically distinct membrane associated pool of this inositol polyphosphate. Our data thus demonstrate that $InsP_6$ is involved in the modulation of pancreatic β-cell signal-transduction, having an essential integral role in membrane trafficking.

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RADIOSENSITIVITY OF PANCREATIC CARCINOMA CELLS. *IN VITRO* AND *IN VIVO* STUDIES

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The objective of this paper was to determine, *in vitro,* the radiosensitivity of a human pancreatic cell line PANC-1 (derived from human pancreatic carcinoma), and the *in vivo* response of tumors to ionizing radiation when cells were inoculated in nude mice.

Cells were seeded in RPMI medium (3500 cells/flask) in triplicate and irradiated 24 h later. The irradiation was performed using an IBL 437C H type equipment calibrated with a TLD 700 dosimeter. The dose range was from 0 to 10 Gy and the number of colonies was scored on day 7 post-irradiation. Using adequate software, survival curves were plotted, fitted to the linear-quadratic model and the radiosensitivity parameters were determined.

Results obtained were: alpha=0.53 ± 0.09 Gy^{-1} and beta=0.18 ± 0.03 Gy^{-2}. When different drugs, such as insulin growth factor type-1 (IGF-1), were added to culture, the radiosensitivity parameters did not show significant difference.

The *in vivo* effect of ionizing radiation was evaluated in tumors induced in nude mice by *s.c.* inoculation of PANC-1 cells. Three groups of mice were employed (n=5 each): A) one group received 2 μg/0.1 ml *s.c.* IGF-1 twice daily, over 4 days, before whole body irradiation with 10 Gy; B) another group of mice was irradiated as A without IGF-1 administration. The results indicate that IGF-1 treatment showed a clear protective effect on the small intestine and bone marrow: the number of intestinal crypts were significantly higher in A *vs* B group and A group showed grade II aplasia *vs* grade III in group B; C) another group of mice, bearing pancreatic tumors *s.c.* developed by inoculation of $3x10^6$ PANC-1 cells, received local ionizing radiation. Radiation was delivered in 1.5 Gy/day fraction over 20 days, using a Rich-Seifert X-ray generator, operating at 0.1 Gy/min. Dose rate was determined according to the OIEA TRS N^0: 277, 1987 Proceedings. The obtained results clearly showed a decreased tumor growth rate due to irradiation ($p=0.0021$). Molecular studies are under way at our laboratory to elucidate the mechanisms of response to ionizing radiation in various types of malignant cells.

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HISTAMINE MODULATES THE ACTIVITY OF ANTIOXIDANT ENZYMES AND ROS PRODUCTION IN HUMAN MALIGNANT CELL LINES

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We have previously reported that histamine (HA) enhances radiosentivity of malignant cells and also protects normal tissues from high doses of ionizing radiation. In order to investigate the molecular mechanism underlying these effects, we evaluated the capacity of HA to modulate the activity of antioxidant enzymes. We studied the action of HA on the cell lines MDA-MB-231 (human breast carcinoma), WM35 (melanoma) and PANC-1 (pancreatic carcinoma). The levels of intracellular reactive oxygen species (ROS) were assessed by flow-cytometric analysis employing specific fluorescent dyes. The activity of the antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), was evaluated in cell extracts by spectrophotometric techniques. HA treatment produced a significant decrease in cell proliferation and this effect was correlated with a marked increase in H_2O_2, while $O_2^{\cdot-}$ levels showed minor changes. The activity of SOD and CAT was significantly modified by HA. HA produced a two-fold