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19. ABSTRACT (Continue on reverse if necessary and identify by block number) During the period under report, we have made significant progress in the studies proposed under various specific aims. More importantly, antibodies to three major gap junction (GJ) proteins were generated and used to characterize the GJ proteins of various tissue culture systems. Progress has also been made in understanding the biochemical and molecular basis of the action of certain tumor promoting chemicals, such as TPA, mezerein and bryostatin, which indicated that protein kinase C (PKC), an import component of cellular second messenger system, was activated. Since gap junction protein is considered to be affected by PKC, the observations we made suggest that PKC activating toxicants can exert their action as tumor promoters through abolishing GJ protein function. Another study suggested that certain oncogenes, ras, neu and src, induce cellular transformation and the resulting transformed cells have very poor GJIC. Studies are underway to identify the mechanisms of gap junction protein regulation.			
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Annual Technical Report

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The Role of Chemical Inhibition of Gap-Junctional
Intercellular Communication in Toxicology

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I. SUMMARY OF PROGRESS TO DATE

During the period of the grant under report, we have essentially continued our efforts to investigate the various aspects of the proposed studies, described under the specific aims. Special emphasis was placed to develop polyclonal antipeptide antibodies to three major connexin (gap junction) proteins in order to identify the changes in their expression under different conditions. Efforts were also directed to understand the biochemical mechanisms of the action of tumor promoters.

Specific Aims

1. Specific Aims 1 and 3. We have now been able to demonstrate that specific promoters, such as TPA, mezerein, bryostatin, but not several organochlorine compounds, were potent activators of protein kinase C (PKC), a calcium and phospholipid dependent kinase. These agents were also potent inhibitors of gap junctional communication. This provided a mechanism by which tumor promoters inhibit GJIC by phosphorylating the gap junction protein.
2. Specific Aim 2. Oncogenic transformation has been a major focus of our research efforts. Three oncogenes, src, ras, and neu, were used to transfect the rat liver epithelial cell line, WBF-344, and rat glial cells (for neu oncogene). The resulting transformed cells have a characteristic morphology of transformed tumorigenic cells. In all cases, there was a significant reduction in the GJIC of these cells, suggesting that a major functional change of these transformed cells was their inability to communicate with other cells and supported our hypothesis that inhibition GJIC contributes to tumorigenesis.
3. Specific Aim 4. In our efforts to identify environmental chemicals as potential toxicants, we have studied a number of chemicals for their ability to inhibit GJIC in a number of cell culture models. The results of these studies further reinforced our contention that down modulation of GJIC reflects the potential of xenobiotics to exert a variety of toxicities. These studies suggested the need to understand the various biochemical mechanisms of action of these chemicals in different responsive cell culture models.
4. Specific Aim 5. A major thrust of our research investigations during this period was in the production of antibodies to gap junction proteins. Highly purified antibodies specific to various types of gap junction proteins are clearly required in order to understand the mechanisms of action of inhibitors of GJIC. Highly purified antipeptide antibodies to 3 major GJ proteins were produced in rabbits and were affinity purified. Immunochemical and Western blotting studies indicated that the

antibodies were very specific to the 26, 32 and 43 KD gap junction proteins and will be very useful to characterize the GJ proteins under different treatment conditions.

5. Specific Aim 6. In the previous grant period, we initiated the isolation and characterization of gap junction deficient mutants of WBF-344 cells. Clearly these mutants will immensely aid us in understanding the role of GJIC in tumorigenesis. We have completed characterization of 5 mutants which are completely deficient in GJIC. These studies are being extended to isolate GJIC mutants from human derived cells.

SUMMARY OF THE PUBLISHED AND UNPUBLISHED RESULTS

A number of publications have resulted from the investigations carried out with the support of the Air Force grant. The summaries of the published papers and abstracts of the results presented at national/international meetings, as well as unpublished results, are presented below.

As evidence that this joint, multidisciplinary, in vitro/in vivo proposal not only has scientific validity but also a practical chance of succeeding, we have summarized the abstracts of several jointly performed experiments. Many of the studies which are the basis for the present proposal have been reported at several meetings. The abstracts of the presentations or published papers are given below.

1. Xenobiotic modulation of Gap Junctional Intercellular Communication in Rat Leydig Cells In Vitro. Helen Hong Xu, J.E. Trosko, B. Lockwood and B.V. Madhukar. Presented at the Annual Meeting of the Society of Toxicology, February 1990, Miami, Florida.

In our continuing efforts to develop in vitro models to study the cellular interactions of toxic xenobiotic chemicals, we have investigated the modulation of gap junctional intercellular communication (GJIC) in a rat Leydig cell culture system. GJIC was measured using a scrape-loading/dye transfer technique and a FRAP technique. GJIC was abolished in these cells following a 1 hour treatment with TPA (10 ng/ml), dieldrin, heptachlor, heptachlor epoxide, and PCB mixture, Arochlor-1254 (10 g/ml). However, DDT, PBB isomers, mirex or lindane did not abolish GJIC of these cells. Compounds which abrogated GJIC showed a dose and time dependent response. Since many of the chemicals which did not affect GJIC in Leydig cells were potent inhibitors of GJIC in other systems the data suggested a cell/tissue specificity of the effect of these chemicals. The data also suggest that inhibition of GJIC by toxic chemicals may be a useful biomarker for identifying potential reproductive/developmental toxicants.

2. Mezerein Inhibition of Intercellular Communication and Activation of Protein Kinase C in Human Kidney Epithelial Cells. W.J. Paradee, B.V. Madhukar and J.E. Trosko. Presented at the Annual Meeting of the Society of Toxicology, February 1990, Miami, Florida.

Inhibition of gap junctional intercellular communication (GJIC) has been implicated as an important epigenetic modulation during tumorigenesis. Many tumor promoters have been documented as potent inhibitors of GJIC. Using a human kidney derived cell culture system we have investigated the down-regulation of GJIC by mezerein, a stage II tumor promoter. Two techniques, a scrape-loading/dye transfer and Fluorescent Reappearance After Photobleaching were used to measure GJIC. Mezerein inhibited GJIC in a dose dependent manner after 1 hour exposure of the cells. concentrations below 0.01 ng/ml were ineffective. A time dependent decrease in GJIC was observed at 10 ng/ml of mezerein. Inhibition was complete at 30 minutes after treatment and was sustained for up to 36 hours. Under similar conditions, mezerein translocated the calcium and phospholipid-dependent protein kinase C (PKC) to the plasma membrane in a dose and time dependent manner in these cells. The sustained membrane association of this enzyme correlated well with the down-regulation of GJIC. The data suggest that activation of PKC may be directly involved in the down-regulation of GJIC by mezerein.

3. Protein Kinase C Translocation during Mezerein-Inhibited Intercellular Communication In Vitro. Heather L. Rupp, J.E. Trosko and B.V. Madhukar. Presented at the Annual Meeting of the Society of Toxicology, February 1991, Dallas, Texas.

A major epigenetic modulation induced by many tumor promoters both in vivo and in vitro is inhibition of gap junctional intercellular communication (GJIC). In the present study, we investigated the correlation between inhibition of GJIC by mezerein, a stage II tumor promoter, and the membrane translocation of the calcium and phospholipid dependent protein kinase C (PKC) in rat liver epithelial culture model WB-F344. The results indicated that mezerein induced the translocation of PKC to the plasma membrane in a time and dose dependent manner (0.1 - 10 ng/ml). However, the membrane association of PKC was reversed after 6 hours and no PKC activity was observed either in the membrane or the cytosol at 24 hours. Under similar experimental conditions, we observed that GJIC was abolished in mezerein-treated cells in a time and dose dependent manner.

The calcium antagonist, TMB-8 (50 μ m), transiently prevented mezerein induced translocation of PKC and down-regulation of GJIC. The data suggested that PKC translocation (activation) is directly involved in the down-regulation of GJIC.

4. Xenobiotic Modulation of Gap Junctional Communication of Rat Pancreatic Epithelial Cells In Vitro. B.V. Madhukar, Heather L. Rupp, William J. Paradee and James E. Trosko. Presented at the Annual Meeting of the Society of Toxicology, February 1991, Dallas, Texas.

In our continuing efforts to develop in vitro systems to study chemical modulators of gap junctional intercellular communication (GJIC), we have investigated the action of several environmental xenobiotics to inhibit GJIC in rat pancreatic epithelial cells. The results indicated that many chlorinated pesticides, the phorbol ester tumor promoter, TPA, and a number of PCBs inhibited GJIC of these cells. The inhibitory action of these chemicals was time and dose dependent. However, the inhibitory action of TPA was transient (less than 6 hours) while that of DDT, dieldrin or heptachlor epoxide was sustained suggesting possible differences in the action of these agents. Concentrations at which TPA (0.1 ng/ml) and dieldrin (1 g/ml) had minimal effect on inhibition of GJIC, these two chemicals showed synergism. These observations suggested that GJIC is modulated by more than one mechanism. TPA induced the translocation of the calcium and phospholipid dependent protein kinase C while DDT, dieldrin or heptachlor epoxide induced a transient increase in intracellular free calcium.

5. Modulated Gap Junctional Communication as a Biomarker for the Multiple Toxicities of Pesticides. James E. Trosko, Burra V. Madhukar, Helen Xu, Emmanuel Dupont and Chia C. Chang. Presented at the NIEHS, July 1990,

The mechanisms by which pesticides cause teratogenic, carcinogenic, neurotoxic, immunotoxic and reproductive toxic effects are not known. In general, the three endpoints of toxic chemical effects are gene and chromosomal mutations (genotoxicity), cell killing (cytotoxicity) and altered gene expression caused by disrupted homeostasis (epigenetic alterations). Homeostasis in multicellular organisms is mediated by extracellular-, intracellular- and intercellular communication mechanisms. Gap junctions, membrane associated protein channels, which allow ions and small molecular weight molecules to pass between contiguous cells, are up-or down-regulated by activated protein kinase C and A, by intracellular changes in pH, Ca⁺⁺ and c-AMP, as well as other undefined mechanisms. A wide variety of chemicals, including many pesticides, and herbicides, have been shown to down-regulate gap junctional communication in various mammalian cell types, including various human cells, at non-cytotoxic levels in vitro. Using scrape-loading/dye transfer and fluorescence re-distribution after photobleaching techniques to measure gap junction function, threshold levels, dose responses, synergistisms with endogenous factors, species and cell-type specificities and reversibility of effects have been seen for the pesticides. The results indicate that most of the toxic effects of pesticides can be explained by their ability to disrupt

homeostasis by down-regulation of gap junctional intercellular communication. Use of molecular probes and antibodies for the major gap junction genes and gene products are now being used to determine at which levels pesticides can affect intercellular communication.

6. Suppression of gap junction gene expression by growth factors and TPA in human epidermal keratinocytes in vitro. Emmanuel Dupont, James E. Trosko and Burra V. Madhukar. To be presented at the International Gap Junction Meeting, June 1991, Asilomar, California.

Gap junctional intercellular communication (GJIC) is a fundamental biological process elicited by many types of cells both in vivo and in vitro. We have previously reported (Carcinogenesis 10:13-20, 1989) the development of a primary normal human keratinocyte (NHEK) model system to study GJIC modulation by Epidermal Growth Factor (EGF), Transforming Growth Factor- (TGF-), and hormones, such as insulin in order to correlate cell growth/differentiation effects to changes in intercellular communication. In the present investigation, we extended these observations to determine the nature of the gap junction gene(s) expressed by NHEK cells in a serum-free defined medium, and their regulation by growth factors and TPA. The data indicated that keratinocytes express the genes for both the Cx43 and Cx26 gap junction proteins. NHEK cells cultured in growth factor containing medium (KGM) caused a significant reduction in the expression of mRNAs for these proteins. However, when the keratinocytes were shifted into the basal medium (KBM) in the absence of growth factors/hormones, there was an enhanced expression of both Cx26 and Cx43 genes within 24 hours. Addition of EGF at 10 or 100 ng/ml to NHEK cells in KBM significantly decreased the expression of Cx43 gene but had little effect on the expression of Cx26 gene. In contrast, TGF- (1 ng/ml) added to KBM had no significant effect in altering the level of Cx43 gene but inhibited the expression of Cx26 gene. Together these two agents synergistically interacted to abolish the expression of both Cx26 and Cx43 genes. A potent skin tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) at 10 ng/ml abrogated the expression of both the GJ genes. However, there was a transient elevation in the expression of Cx26 gene at 2 hours post-treatment with 100 ng/ml TPA which lasted for up to 18 hours. Fetal bovine serum (10%), which is known to induce terminal differentiation of keratinocytes also abolished the expression of the two gap junction genes in these cells. Taken together these data suggest that selective suppression of gap junction genes may be associated with both cell proliferation and differentiation of human keratinocytes.

Re-establishment of GJIC in a non-tumorigenic HeLa-normal cell hybrid (manuscript in preparation): In a collaborative study with Dr. Eric Stanbridge of the University of California at Los Angeles, we have demonstrated that hybridization of tumorigenic HeLa cells with normal human fibroblasts resulted in re-establishment of gap junctional communication of the hybrid cells and loss of tumorigenicity. These studies have provided strong support to the hypothesis that restoration of functional gap junctions in tumor cells can abrogate their tumorigenic potential (Appendix 3).

Role of protein kinase C in the inhibition of GJIC: In recent years, studies by several workers have addressed the possible role of inositol phospholipid second messenger system in cellular regulation. The two components of this system, diacylglycerol (DAG) and inositol triphosphate (IP₃) are produced following hydrolysis of phosphatidyl inositol biphosphate (PIP₂) by phospholipase C. DAG is an activator of protein kinase C (PKC) while IP₃ affects endoplasmic reticulum to release the intracellular pools of calcium. Both PKC and intracellular free calcium have been shown to inhibit GJIC. Therefore, environmental non-genotoxic chemicals which can influence this PIP₂ second messenger pathway can also modulate GJIC. In our recent studies we have shown that chemicals which activated PKC also blocked GJIC in a manner that loss of GJIC was dependent on membrane association of PKC. Using a confocal image analysis technique of ACAS-570 system, we have been able to localize the translocation of PKC in WB-rat liver epithelial cells treated with a tumor promoter, mezerein. These preliminary studies will be extended to other chemicals and cell culture models to establish the PKC down-regulation of GJIC (Fig. 1 of Appendix 1).

Studies on transcription and/or translational regulation of gap junction proteins: In order to understand the mechanisms of xenobiotic regulation of GJIC, we have carried out preliminary studies to identify the molecular events regulating GJ proteins in growth factor treated and oncogene transfected cells. These studies indicated that there was a time dependent loss of GJ mRNA in either EGF, TGF- or TPA-treated primary human keratinocytes. In V-Src oncogene transfected WB-rat liver cells, there was an increase in the expression of Cx32 RNA indicating induction of differentiation of WB cells by src-oncogene transfection, while the major GJ protein, Cx43, was found to be proteolytically degraded (Figs. 2 and 3 of Appendix 1). Thus, these preliminary investigations suggest that various agents interfere at different stages in the expression of gap junction proteins in different cell types. These studies will be extended in Specific Aim 3 of the current proposal. It is expected that these molecular/biochemical studies will provide key insights into the altered regulation of GJIC by cellular interactions of toxic chemicals.

Production of antibodies to synthetic peptides of gap junction proteins and characterization of gap junction proteins: One of the Specific Aims of the previous proposal was to generate anti-peptide antibodies unique to the major gap junction proteins, Cx43, Cx32 and Cx26. We have been able to generate the anti-peptide antibodies in rabbits which specifically identify the above 3 types of gap junction proteins. They have been purified by affinity chromatography. These antibodies will enable us to identify the major connexons in various in vitro models and the changes in connexon type expression by xenobiotics (Fig. 4 of Appendix 1). Thus, having these antibodies, we are in a unique position to study the events in the regulation of GJIC by chemicals. They will be used in many studies proposed in the current grant.

A number of publications have resulted from studies supported by this grant during the last 2 years (1989-90). The papers which are either already published, or in press or in preparatory stage are listed below. Reprints and/or preprints of some of these publications are submitted as Appendices.

1. Published Papers

- Madhukar, B.V., Oh, S.Y., Chang, C.C., Wade, M. and Trosko, J.E. (1989) Altered regulation of intercellular communication by epidermal growth factor, transforming growth factor-Beta and peptide hormones in normal human keratinocytes. *Carcinogenesis* 10:13-20.
- Trosko, J.E. and Chang C.C. (1989) Stem cell theory of carcinogenesis. *Toxicol. Letters* 49:283-295.
- Trosko, J.E. and Chang, C.C. (1990) Gap junctional intercellular communication in neoplasia: Implications for the cause and treatment of cancer. In: Familial Adenomatous Polyposis. Alan R. Liss, Inc., pp. 279-288.
- Trosko, J.E., Chang, C.C. and Madhukar, B.V. (1990) Cell-to-cell communication: Relationship of stem cells to the carcinogenic process. In: Mouse Liver Carcinogenesis: Mechanisms and Species Comparisons. Alan R. Liss, Inc., pp. 259-276.
- Kuslikis, B.I., Trosko, J.E. and Braselton, W.E. (1991) Mutagenicity and effect on gap-junctional intercellular communication of 4,4'-methylenebis(2-chloroaniline) and its oxidized metabolites. *Mutagenesis* 6:19-24.
- Trosko, J.E., Chang, C.C., Madhukar, B.V. and Oh, S.Y. (1990) Modulators of gap junction function: The scientific basis of epigenetic toxicology. *In Vitro Toxicol.* 3:9-26.

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- Trosko, J.E. and Chang, C.C. Chemical tumor promoters, oncogenes and growth factors: Modulators of gap junctional intercellular communication. In: The Pharmacological Effect of Lipids III, Role of Lipids in Cancer Research. J.J. Kabara et al. (eds.), The Am. Oil Chemists' Society, Champaign, IL, pp. 107-115.
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- Hasler, C.M., Frick, M.A., Bennink, M.R. and Trosko, J.E. (1990) TPA-induced inhibition of gap junctional intercellular communication is not mediated through free radicals. *Toxicol. Appl. Pharmacol.* 103:389-398.
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- Madhukar, B.V., Trosko, J.E. and Chang, C.C. (1989) Chemical, oncogene and growth factor modulation of gap junctional communication in carcinogenesis. In: Cell Interactions and Gap Junctions. N. Sperlakis and W.C. Cole (eds.), CRC Press, Inc., Boca Raton, FL, vol. I, pp. 143-157.
- Trosko, J.E. and Chang, C.C. (1990) Stem cell theory of carcinogenesis. *Proc. 18th Natl. Conf. Toxicol.* 11/88, H.G. Armstrong Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, OH, pp. 217-230.

2. Manuscripts submitted or in preparation

- Kalimi, G.H., Chang, C.C., Edwards, P., Dupont, E., Madhukar, B.V., Stanbridge, E. and Trosko, J.E. (1991) Re-establishment of gap junctional communication in a non-tumorigenic HeLa-normal human fibroblast hybrid (in preparation).
- Oh, S.Y., Madhukar, B.V., Chang, C.C., Trosko, J.E. and Beyer, E. (1991) Characterization of gap junctional communication deficient (GJIC) mutants from a hypoxanthine-guanine phosphoribosyl transferase (HGPRT) rat liver epithelial cell line (manuscript in revision after additional experiments).
- Hshu, H., Trosko, J.E. and Madhukar, B.V. (1991) Xenobiotic inhibition of intercellular communication in rat leydig cells in vitro (in preparation for In Vitro Toxicol.).
- Paradee, W.J., Madhukar, B.V. and Trosko, J.E. (1991) Mezerein inhibition of intercellular communication in human kidney epithelial cells: Correlation with sustained membrane association of protein kinase C (in preparation for Biochem. Biophys. Res. Commun.).
- Madhukar, B.V., de Feijter, A.W., Hasler, C.M., Lockwood, B., Oh, S.Y., Chang, C.C., Stanbridge, E. and Trosko, J.E. (1991) Characterization of an in vitro human kidney epithelial system to study gap junctional intercellular communication. In Vitro Toxicol. (accepted for publication).
- Madhukar, B.V., Oh, S.Y., Quensen, J., Wade, M., Jiwa, A.H. and Trosko, J.E. (1991) Inhibition of intercellular communication and regulation of intracellular calcium by dieldrin, heptachlor and heptachlorepoide in a rat liver epithelial cell line in vitro (in preparation for submission to J. Cell. Physiol.)
- Rupp, H.L., Oh, S.Y., Madhukar, B.V. and Trosko, J.E. (1991) Transient membrane association of protein kinase C temporally correlates with inhibition of intercellular communication by mezerein in rat liver epithelial cells (in preparation for submission to J. Cell Biol.)