gen receptors) approaches will be described that will be useful in assessing the impact of estrogenic compounds (e.g., phytoestrogens,) and other known or suspected endocrine disrupting chemicals on the development and function of these sexually dimorphic brain areas. (Supported by and Interagency Agreement between FDA & NIEHS.)

1954 NEUROPROTECTIVE ACTIONS OF ESTROGEN IMPLICATIONS FOR EXPOSURE TO ESTROGENIC CHEMICALS.

D B Miller[1], J P O'Callaghan[1], E A Johnson,[1] and S F Ali[2]. [1]*Toxicology & Molecular Biology Branch, Health Effects Laboratory Division, CDC/NIOSH, Morgantown, WV;* [2]*Neurochemistry Laboratory, Division of Neurotoxicology, NCTR/FDA, Jefferson, AR, USA.*

The recent focus on the hormone-like effects of many xenobiotics has led to a renewed interest in both the reproductive and nonreproductive actions of estrogen. Its protective or age-retardive actions are well established for multiple body systems including skin, bone and teeth, colon, blood vessels and heart. Clinical and epidemiological studies suggest neuroprotective properties in Parkinson's and Alzheimer's disease. *In vitro* and *in vivo* experimental data indicate estrogen may prevent the neuronal cell damage and necrosis observed following excitotoxic, metabolic and oxidative insult. Conversely, protracted estrogen exposure whether due to age or exogenous administration damages certain brain areas. Mechanisms mediating these protective or pathological actions may include activation of pathways or release of substances through specific intracellular receptor-mediated actions; direct, rapid, nongenomic effects at the cell membrane, at membrane receptor sites and ion channels or at cyclic AMP response elements; altered metabolic profile of critical brain enzymes; and alteration of neurotransmitter and neuropeptide transmitter mechanisms in brain. Utilization of transgenic technology has been useful in elucidating the mechanism of estrogen's protective effects in the vasculature and bone and should be useful in examining its CNS protective and pathological actions. Whether compounds with estrogen agonist, antagonist or mixed actions (e.g., tamoxifen, phytoestrogens, triphenylethylenes) can interfere with or mimic the neuroprotective or neuropathological actions of estrogen has received little scrutiny or debate. Tamoxifen can, however, block some but not all of the neuroprotective actions of 17α or β -estradiol *in vitro* and can modulate certain aspects of nigral striatal function including release of dopamine in response to stimulation and the response to dopaminergic neurotoxic insult. Actions of other estrogenic agents in these models is unknown. (Supported by CDC/NCTR.)

1955 NEUROPROTECTIVE ROLE OF ESTROGEN IN OXIDATIVE STRESS INDUCED NEURODEGENERATION: IMPLICATIONS FOR NEUROTOXIC INSULT.

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Certain neurodegenerative diseases like Parkinson's disease, affect more men than women and women with Alzheimer's disease receiving hormone replacement therapy show a lessened severity and slowed disease progression. Estrogen may have antioxidant properties as these diseases are linked to oxidative damage. *In vitro* studies utilizing neural tissue have shown that 17β -estradiol can decrease excitotoxic damage by directly inhibiting the NMDA receptor and limit the damage caused by β -amyloid peptides, a suspected etiological agent in Alzheimer's disease. In examining the striatal dopaminergic neurotoxicity of agents such as MPTP and methamphetamine (METH) that are suspected to cause neuronal injury by oxidative stress, greater dopaminergic neurotoxicity was noted in males. Evidence linking estrogen to this gender difference was provided by the finding that ovariectomized (OVX) mice, compared to mice receiving 17β -estradiol, displayed greater striatal damage in response to MPTP suggesting that estrogen has neuroprotective properties in this model of striatal dopaminergic neurotoxicity. Protection was not linked to alterations in metabolism or generation of the proximal toxicant although estrogen is known to affect metabolic processes. Similar neuroprotective effects of estrogen were found for METH-induced dopaminergic neurotoxicity and others have reported greater striatal damage in OVX female rats receiving 6-hydroxydopamine, another dopaminergic neurotoxicant suspected to damage tissue through a free radical/oxidative stress mechanism. Whether other estrogenic compounds, including tamoxifen, the triphenylethylenes, and the phytoestrogens, can mimic or disrupt the neuroprotective actions of estrogen has received limited examination or discussion. (Supported by NCTR/CDC.)

1956 COMPLEMENT ACTIVATION IN TRIMELLITIC ANHYDRIDE (TMA)-INDUCED PULMONARY HYPERSENSITIVITY IN THE GUINEA PIG.

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TMA is a small molecular weight compound known to cause hypersensitivity reactions in the lung, particularly occupational asthma. Actively sensitized guinea pigs challenged intratracheally with TMA conjugated to guinea pig serum albumin (TMA-GPSA) respond with an immediate bronchoconstriction and delayed eosinophil, neutrophil and mononuclear cell infiltration into the lungs and lung hemorrhage. These events are usually attributed to antigen interaction with mast cell antibody. However, our previous studies using Cobra venom factor to deplete complement indicated a role for the complement system in delayed cellular infiltration into the lungs and lung hemorrhage (Journal of Pharmacology and Experimental Therapeutics 273:793-801, 1995). Thus, we hypothesized that the complement anaphylatoxins C3a and C5a were the relevant products of complement system activation mediating the cellular infiltration and lung hemorrhage. The purpose of the present study was to determine if the complement system activation product C3a was produced in the bronchoalveolar lavage (BAL) fluid of actively sensitized guinea pigs in response to challenge with TMA-GPSA. Guinea pigs were sensitized intradermally with TMA in corn oil. Three weeks later animals were challenged by intratracheal instillation of either TMA-GPSA (n=33) or GPSA (n=28). Twenty-four hours after challenge, the guinea pigs were anesthetized with pentobarbital and the lungs lavaged with phosphate buffered saline. Complement activation product C3a was measured in the BAL fluid by Western blot and immunodetection. The quantity of C3a in the BAL fluid of TMA-GPSA challenged animals was significantly greater than that found in GPSA challenged guinea pigs ($p<0.01$). Our finding of increased C3a is consistent with a potential role for complement anaphylatoxins in TMA-induced cellular infiltration and lung hemorrhage. (Supported by NIH ES 07406.)

1957 ASSESSMENT OF RESPIRATORY SENSITIZING POTENTIAL OF ACID ANHYDRIDES BY CYTOKINE FINGERPRINTING.

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We have demonstrated previously that contact allergens such as 2,4-dinitrochlorobenzene (DNCB) and respiratory allergens such as trimellitic anhydride (TMA) induce discrete type 1 and type 2 cytokine secretion patterns, respectively, following prolonged topical exposure of BALB/c strain mice. These observations have formed the basis of an approach to the identification of respiratory allergens known as 'cytokine fingerprinting'. We have now compared the patterns of cytokine production by TMA- and DNCB-activated draining lymph node cells (LNC) with those provoked by concurrent treatment with a number of additional acid anhydrides which have been implicated as potential occupational respiratory sensitizers. These comprised maleic anhydride, hexahydrophthalic anhydride and phthalic anhydride. Under immunogenic conditions of exposure, determined as a function of the induction of significant lymphocyte proliferation in draining nodes, all of the selected acid anhydrides stimulated a type 2 cytokine secretion phenotype. In each case interleukin 10 expression reached comparable levels to those provoked by the reference respiratory allergen TMA. Detectable mitogen-inducible interleukin 4 (IL-4) was also induced, although levels were generally much lower than those elicited by TMA. In contrast DNCB-activated LNC failed to produce detectable levels of these cytokines. Low expression of the type 1 cytokines interferon γ and interleukin 12 was observed in response to treatment with the acid anhydrides, compared with the substantial production of these cytokines by LNC cultured from DNCB-exposed mice. These data provide further confirmation that cytokine fingerprinting represents a robust and reliable approach for the identification of potential respiratory allergens.

1958 TRIMELLITIC ANHYDRIDE (TMA) HYPERSENSITIVITY IN MICE AFTER DERMAL EXPOSURE AND INTRATRACHEAL (IT) CHALLENGE.

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TMA causes Th2 related respiratory (RH) and Th1 related contact hypersensitivity (CH) responses. Elevated total serum IgE has been reported after

An Official Journal of the
Society of Toxicology
Supplement

38th ANNUAL MEETING

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology

The Toxicologist

Oxford University Press

Volume 48, Number 1-S, March 1999

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology

Published by Oxford University Press, Inc.

Abstracts of the 38th Annual Meeting

Volume 48, Number 1-S

March 1999