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16. Abstract (Limit: 200 words) The relationship between the neuropathy target esterase (NTE) to organophosphorus (OP) compound interaction and the fate of retrograde transport of iodine-125 labeled tetanus-toxin was studied in hen sciatic nerve following a single subcutaneous injection of either a neurotoxic OP compound, a nonneurotoxic OP compound, or paraoxon (311455). In order to induce central peripheral distal axonopathy in these hens, a greater than 80 percent phosphorylation and subsequent intramolecular rearrangement of NTE in the nerve fiber were required. A progressive decrement of retrograde axonal transport in sensory and motor fibers that culminated, days later, in axon degeneration, was caused by suprathreshold biochemical reaction a few hours after dosing. Seven days after neurotoxic OP dosing the maximum transport deficit was reached; this was prior to the onset of nerve fiber degeneration and clinical signs of neuropathy. No effect on axon transport, nerve fiber integrity or clinical status was caused by nonneurotoxic OP. Paraoxon did not inhibit NTE and did not cause either deficit in retrograde transport or neuropathy. The author conclude that alterations in retrograde axonal transport may be important in the pathogenesis of nerve fiber degeneration in this and related toxic neuropathies.

17. Document Analysis a. Descriptors

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Final Progress Report

NEUROTOXIC ESTERASE AND NEUROTOXICITY

SUMMARY STATEMENT

A single exposure of susceptible species, including Man, to certain organophosphorus compounds (OP) induces a delayed onset of peripheral neuropathy associated with distal axonal degeneration of peripheral nerves and long spinal tracts. The initial event, occurring within hours of dosing, is the phosphorylation and "aging" of a target protein (NTE: Neuropathy Target Esterase), but the relationship between this event and the delayed onset of axon degeneration is unknown. The objective of this project was to determine whether the OP-NTE reaction is followed by detectable pathophysiological changes that precede the onset of the first morphological or neurobehavioral abnormality in the test animal (hen) with specific focus on the fate of retrograde axon transport, a critical interneuronal communication that seems to be exceptionally vulnerable in some toxic neuropathies.

PROGRESS AND ACCOMPLISHMENTS

METHODOLOGY:

The relationship between NTE/OP interaction and the fate of retrograde transport of ^{125}I-tetanus toxin (a marker protein) was examined in hen sciatic nerve after a single, subcutaneous injection of either neurotoxic (DBDCVP) or non-neurotoxic (PMSF or paraoxon) compounds. DBDCVP is a neuropathic agent which inhibits/"ages" NTE and also inhibits acetyl-cholinesterase (unrelated to neuropathy induction); PMSF inhibits but does not "age" NTE; paraoxon, diethyl-p-nitrophenylphosphate, inhibits acetylcholinesterase only. At selected intervals after receiving one of these compounds, animals were administered a single intramuscular (gastrocnemius) injection of ^{125}I-tetanus toxin. Retrograde axonal transport of radiolabel was subsequently assessed by determining the amount of ^{125}I transported to lumbar dorsal root ganglia (sensory axons) and ventral spinal cord (motor axons). Control animals were treated with comparable doses of PMSF or paraoxon to determine if defective transport is related to NTE inhibition/"aging."

ACCOMPLISHMENTS:

The induction of central-peripheral distal axonopathy in hens singly dosed with some organophosphorus (OP) compounds, such as DBDCVP, requires greater than 80% phosphorylation and subsequent intramolecular rearrangement ('aging') of NTE in the nerve fiber. Suprathreshold biochemical reaction a few hours after dosing was shown to cause a progressive decrement of retrograde axonal transport in sensory and motor fibers that culminates, days later, in axon degeneration. The maximum transport deficit (about 70% reduction) was reached 7 days after DBDCVP (0.75-1.00 mg/kg s.c.) prior to the onset of nerve fiber degeneration and clinical signs of neuropathy. By contrast, PMSF (30 mg/kg s.c.), an agent that prevents the development of OP neuropathy by inhibiting NTE without the aging reaction, had no effect on axon transport, nerve-fiber integrity and clinical status when administered either alone or prior to a neurotoxic dose of DBDCVP. Paraoxon (0.2

mg/kg s.c.) did not inhibit NTE and was also unable to cause either deficit in retrograde transport or neuropathy. Taken in concert, these studies demonstrate that retrograde transport deficit is correlated with the threshold-initiating mechanism in OP-induced nerve fiber degeneration. The effect of DBDCVP on retrograde axonal transport is selective and not a consequence of other known major changes in the physiology of the axon.

SIGNIFICANCE:

Peripheral neuropathy is a remarkably common reponse of the human nervous system to systemic intoxication with occupational chemicals, including certain OP compounds, acrylamide, n-hexane, methyl n-butyl ketone, carbon disulfide, and dimethylaminopropionitrile. The neuropathies induced by these agents are all associated with distal axon degeneration of long and large-diameter nerve fibers in peripheral nerves and long tracts of the spinal cord. The mechanisms underlying axonal degeneration in OP neuropathy have been illuminated by the results of this project which indicate that alterations in retrograde axonal transport may play an important role in the pathogenesis of nerve-fiber degeneration in this and related toxic neuropathies.

PUBLICATIONS RESULTING FROM THIS GRANT:

Moretto A, Lotti M, Sabri MI and Spencer PS: Reduced retrograde transport heralds OP axonopathy. Trans Am Soc Neurochem, in press

Spencer PS, Sabri MI, Moretto A and Soiefer A: Chemical probes of neuroaxonal dystrophy. Int Symp on Neuroaxonal Dystrophy and Axonal Transport, Abst, Feb 19-21, 1986, Washington, D.C.

Spencer PS and Schaumburg HH: Chemical neurotoxicity. In Diseases of the Nervous System (ed. Asbury, A.K., McKhann, G., McDonald, I.). Heineman, London, in press

Spencer PS, Arezzo JC and Schaumburg HH: Chemicals causing disease of neurons and their processes. In: Neurotoxicity of Industrial and Commercial Chemicals (ed. O'Donoghue, J.), CRC Press, Boca Raton, pp1-4, 1985

Spencer PS, Miller MS, Ross SM, Schwab B and Sabri MI: Biochemical mechanisms underlying primary axonal degeneration. In: Handbook of Neurochemistry (ed. Lajtha, A.), vol. 9., Plenum Press, New York, pp31-65, 1985

Moretto, A, Lotti M, Sabri MI and Spencer PS: Progressive deficit of retrograde transport is involved in the pathogenesis of di-n-butyl dichlorvos axonopathy. J Neurochem, in press.

EQUIPMENT INVENTORY

No equipment was acquired under this award.