THE NEUROTOXICOLOGY AND PATHOLOGY OF ORGANOMERCURY, ORGANOLEAD, AND ORGANOTIN

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INTRODUCTION

Metal ions exist in our everyday environment - food, water, and air. Many of the metallic elements, such as calcium, magnesium, and zinc, are essential to the well-being of our health; others, such as mercury, lead, and tin, particularly their organic compounds, are hazards to human health.

The objective of the present review is to provide an overview of the neuropathological impact of some of these toxic organometals - including mercury, lead, and tin which are known to be neurotoxic to animals and to man.

ABSTRACT

The toxicities of many metals, such as mercury and lead, are known to man since the dawn of civilization. Organic compounds of some heavy metals are known to have a particular toxic impact on the central nervous system. Organomercury, particularly alkyl-mercuric compounds (e.g. methylmercury), has a selective effect on the granule cells of the cerebellum, the nerve cells of the calcarine cortex, and the sensory neurons in the dorsal root ganglia. The well known Minamata Bay disease is the result of a massive epidemic episode of human exposure to alkylmercury contaminated food sources. Mental retardation and other developmental defects are also known to be a consequence of exposure to this toxic metal. Organic lead compounds have been employed as gasoline additives and in other industrial purposes. Unlike its inorganic counterpart, organolead compounds have a more prominent impact on the central nervous system. Pathological changes of the brain stem neurons have been described. Organotin compounds have been used in plastic industries and as agricultural chemicals. Both trimethyl and triethyl tin compounds are found to be extremely neurotoxic. Despite

the similarity of their chemical structures, trimethyl and triethyl tins have a diversely different toxic property and effects. While triethyl tin is myelinotoxic, producing edematous and vacuolar changes in the central myelin, trimethyl tin is neuronotoxic, producing prominent toxic changes in the neurons of the limbic system (hippocampus, entorhinal cortex, etc.). The factors which determine the specificity and selectivity of the neurotoxic impacts by various organometals are still unknown. In view that most of the organometals are still widely employed by many countries for industrial and for agricultural purposes, caution must be made for their proper handling and disposal to avoid undesirable exposures to workers and environmental contamination of water sources and food-chain for the common public. Since organometals are difficult to eliminate from the central nervous system, injuries usually lead to permanent neurological deficits, such tragedies are frequently long lasting and create not only a medical problem, but also a social economical problem for the society.

ORGANOMERCURY

Mercury is one of the oldest known toxic metals to man. Among all mercury compounds, organomercurials, particularly methylmercury (alkylmercury), have the most potent toxic impact on the nervous system.

Since the outbreak of Minamata disease (methylmercury poisoning) in Japan in the early 1950s (Takeuchi *et al.*, 1959, 1962a,b), mercury, particularly methylmercury, has been recognized as an extremely hazardous environmental pollutant (Katsuki *et al.*, 1957; Tokuomi, 1961; Tokuomi *et al.*, 1966; Okinaka *et al.*, 1964; Bache *et al.*, 1971).

General Clinicopathologic Findings in Minamata Disease

Since the outbreak of Minamata disease in Japan, many excellent reviews on the pathological and clinical findings on this disease have been published (Takeuchi, 1968, 1970; Takeuchi *et al.*, 1968). Therefore, the present review will only include a very brief summary on the main clinicopathologic findings in human cases.

The general clinical signs and symptoms observed in human cases of Minamata disease are summarized in Table I.

In chronic cases, atrophy of the brain and hydrops *es vacuo* were observed. In almost all cases, there was gross atrophy of the cerebellar folia, particularly those in the lateral lobes and the vermes and in the calcarine cortices.

Pathological changes in the cerebellar cortex with loss of the granule cells, usually adjacent to or below the Purkinje cell layer, particularly around the depth of the sulci, were observed. Although the Purkinje cells were more resistant, they usually also disintegrate in chronic cases. Proliferation of Bergmann's glia was a common finding. Except for some thinning of myelin and gliosis, no remarkable pathology was found in the white matter.

TABLE I

Frequency of Clinical Signs and Symptoms in Minamata Disease

Symptom or sign	Frequency (%)
Constriction of visual fields	100
Sensory disturbance	100
Ataxia	94
Impairment of speech	88
Impairment of hearing	85
Impairment of gait	82
Tremor	76
Mental disturbance	71
Exaggerated tendon reflexes	38
Hypersalivation	24
Hyperhydrosis	24
Muscular rigidity	21
Ballism	15
Chorea	15
Pathologic reflexes	12
Athetosis	9
Contractures	9

Lesions in the calcarine cortex along the depth of the calcarine fissure were predominantly involved. There was degeneration of nerve cells and myelin sheaths, particularly in the second and upper-third layers. Astrocytosis, glial fiber proliferation and tissue disruption were variably demonstrable.

Experimental Methylmercury Intoxication

Despite the large variations in experimental designs (different species employed, chronicity in toxicity, etc.), the basic neurotoxicity and pathological pattern induced by methyl-mercury is still comparable with that observed in human cases.

Brown and Yoshida (1965), using young chicks, reported cerebellar changes after exposure to diethyl mercury and methylmercury nitrate. The earliest change was found to be dilation and disintegration of the endoplasmic reticulum and Golgi complex in both Purkinje cells and granule cells. These investigators proposed that the organic mercury altered cell membrane structures mainly, and appeared to interfere with protein production in these nerve cells. Such an interpretation was supported by chemical findings of other investigators (Yoshino *et al.*, 1966; Steinwall, 1969; Steinwall and Synder, 1969; Cavanagh and Chen, 1971b; Chang and Hartmann, 1972c; Chang *et al.*, 1972a,b).

In methylmercury poisoning, there was a histologically characteristic disappearance of granule cells which took place at first under the Purkinje cell layer (Morikawa, 1961), particularly affecting those cells at the depth of the sulci. Ultrastructurally, the granule cells appeared atrophic with an increased number of lysosomes (Miyakawa and Deshimaru, 1969). Most degenerating granule cells appeared to be very electron dense, having a coagulated appearance. As observed by Brown and Yoshida (1965), stackings of agranular endoplasmic reticulum could be observed in many Purkinje cells. Contrary to Miyakawa and Deshimaru's report, however, degeneration of the Purkinje neurons as well as the granule neurons was found by Chang and Hartmann (1972a).

The sensory neurons of the dorsal spinal ganglia were found to be extremely sensitive to the toxicity of mercury (Chang and Hartmann, 1972a,b). Such observation was later confirmed by Herman *et al.* (1973), who studied the effects of methylmercuric hydroxide on the sensory glia of the rat. Various changes of the neuronal organelles which included disintegration of endoplasmic reticulum and ribosomes were observed. Such morphological findings further support the reduction of

RNA (Chang et al., 1972a,b) and protein synthesis (Yoshino et al., 1966; Cavanagh and Chen, 1971b) in nerve cells after mercury intoxication.

Degenerative changes of the nerve fibers were also extensively investigated by several investigators (Miyakawa et al., 1970, 1971; Cavanagh and Chen, 1971a; Chang and Hartmann, 1972b; Herman et al., 1973). It was found that the sensory fibers were extremely sensitive and vulnerable to mercury intoxication and that the ultrastructural pattern of degeneration was very similar to that of Wallerian degeneration.

After CH₃HgCl poisoning, however, the myelin sheaths seemed to have lost their lamination (Miyakawa et al., 1970; Chang and Hartmann, 1972b) and acquired a smudged or solid appearance. Extensive axoplasmic accumulation of lysosomes and axoplasmic debris and myelin destruction were the most prominent lesions observed in these nerve fibers. Marked pathological changes were often observed at the nodes of Ranvier.

Miyakawa et al. (1970) described many Schwann cells to be hyperfunctional after mercury poisoning. Layerings of myelin forming concentric figures or membranous structures were frequently observed in many nerve fibers (Chang and Hartmann, 1972b). These observations seem to indicate a phenomenon where degeneration of the parenchymal tissue (axon) is accomplished by hyperreactive response of the supporting elements (Schwann cells). The Schwann cells were also found to play an important role as phagocytes (Chang and Hartmann, 1972b) during the regenerative phase of the nerve fibers after mercury intoxication (Miyakawa et al., 1971).

Experimental Fetal Methylmercury Poisoning

Methylmercury is found to have a potent toxic impact on the developing nervous system. Two detailed reviews on this subject have been made recently by this author (Chang, 1984a; Chang and Annau, 1984) and therefore will not be further elaborated at the present time. Only a brief synopsis of the neuropathological aspect of fetal methylmercury poisoning will be presented.

Congenital malformations are another frequent manifestation of methylmercury's impact on developing organisms. The most common malformations produced in experimental animals have been cleft palate (Spyker and Smithberg, 1972; Su and Okita, 1976), limb defects (Harris et al., 1972), and brain and facial malformations (Spyker and Smithberg, 1972; Gilani, 1975).

The neuropathological lesions resulting from experimental fetal methylmercury poisoning were initially reported in the Japanese literature (Moriyama, 1967; Tatetsu and Harada, 1968; Murakami, 1972). The most severe methylmercury-induced congenital abnormalities are exencephaly and encephalocele (Spyker and Smithberg, 1972; Gilani, 1975). Hydrocephalus has also been observed by several authors (Harris *et al.*, 1972; Murakami, 1972). The type or cause of the hydrocephalus was not described.

Light microscopic studies revealed loss of neurons and cytoarchitectural changes in the cerebrums of rat pups exposed to 5 mg/kg methylmercury on gestational days 0-12 (Murakami, 1972). Cystic changes and small hemorrhages in the cortex and white matter were also observed (Tatetsu and Harada, 1968) following exposure to 1 mg/kg throughout gestation. In the cerebellum, delayed migration of the external granular cell layer was observed in mice following exposure to 1 mg/kg on gestational days 6-17 (Khera and Tabacova, 1973; Reuhl *et al.*, 1981a,b). Alterations of cerebral and cerebellar architecture, with hypoplastic and atrophic neurons and incomplete granular cell layer formation, have also been reported in cats following chronic methylmercury poisoning during gestation (Harada, 1978; Khera, 1973).

Chang *et al.* (1977a,b) reported the first detailed ultrastructural evidence of cellular damage in the brains of mice and rats prenatally exposed to low doses of methylmercury during gestation. In the cerebellum, both Purkinje and granular cell neurons contained abnormal accumulations of lysosomes. Disorientation and shortening of the rough endoplasmic reticulum was seen in Purkinje cells. Occasional neurites contained dilated saccules resembling smooth endoplasmic reticulum, and segmentally incomplete myelination of axons was frequently encountered. Large cytosomes, floccular degeneration, and neuronal necrosis were common. More detailed information concerning the toxic effects of mercury on the developing nervous system may be obtained from the recent review by Chang and co-workers (Chang, 1984a; Chang and Annau, 1984).

Pathogenetic Mechanism of Organic Mercury Induced Neuropathology

Since the blood-brain barrier constitutes the immediate "gateway" between the blood vessels and the nervous system, it becomes important to consider the influence of mercury on this system during chronic mercury poisoning. Steinwall and co-workers (1966, 1969) have shown that an impairment of the blood-brain barrier occurred within hours after the administration of a mercury compound either as mercuric chloride,

methylmercuric chloride, or methylmercuric dicyandiamide via direct perfusion through the carotid artery. By means of light and electron microscopy, Chang and co-workers have also demonstrated that when mercury ions are absorbed into the blood stream, though in minute amounts (1.0 ppm), they are capable of impairing the blood-brain system within hours, leading to an extravasation of normally barred plasma solutes (Chang and Hartmann, 1972d; Ware *et al.*, 1974).

The blood-brain barrier is presently considered to be a complex of multiple systems regulating the exchange of metabolic material between brain and blood (Broman, 1967; Steinwall, 1961; Tower, 1962; Lajtha, 1962; Steinwall and Klatzo, 1966). Therefore, the blood-brain barrier acts by no means merely as a physical barrier; it also acts as an active site for the regulation of the uptake of biological metabolites from the blood to the nervous system (Lajtha, 1962; Broman and Steinwall, 1967). It is conceivable, therefore, that the impairment of the blood-brain barrier, together with the possible inhibition of certain associated enzymes by the mercury, will certainly affect the metabolism of the nervous system.

Subcellular distributional study indicates that the distribution of mercury in general is: mitochondrial fraction > mixed cytoplasmic fraction (endoplasmic membranes) > nuclear fraction (Yoshino *et al.*, 1966; Norseth, 1967; Massey and Fang, 1968). There was a gradual increase in the mercury content in the supernatant fraction as the intoxication progressed. Such observation is later confirmed by electron-microscopic histochemical methods showing that mercury is localized mainly on the biological membranes of the organelles (mitochondria, endoplasmic reticulum, nuclear envelope, etc.) (Chang and Hartmann, 1972c). Biochemical analysis reveals a definitive disturbance in the glycolytic enzyme system (Paterson and Usher, 1971; Salvaterra *et al.*, 1973), a decreased Stage 3 respiration of the mitochondria (Verity *et al.*, 1975), and an early reduction of both RNA (Chang *et al.*, 1972) and protein synthesis (Yoshino *et al.*, 1966; Steinwall, 1969; Steinwall and Snyder, 1969; Cavanagh and Chen, 1971b) in the nerve cells following mercury intoxication.

The toxicity of mercury on the nervous system was shown to be markedly reduced by selenium (Chang *et al.*, 1976, 1977) as well as by vitamin E (Chang *et al.*, 1978). Both of these compounds are associated with antioxidation activities. These observations lead to the theory that free-radical production may be associated with cellular and membrane damages by mercury (Ganther, 1978; Chang and Suber, 1982). Further research in such possibility is needed to explore the mechanism of toxicity of mercury.

In summary, the basic mechanism of mercury induced neuronal damage may be derived from: (1) free radical formation which in turn is injurious to cells and their components; (2) blood-brain barrier dysfunction which leads to irregularity of neural metabolism; (3) metabolic disturbance due to the effect of mercury on various enzymatic systems (e.g. glycolytic pathway) and synthetic mechanisms (e.g. RNA and protein) in the cells; (4) destruction of the cellular protein or membrane in situ; and (5) alterations on the neurotransmitter systems of the nervous system. Either one or a combination of these factors could occur within the nervous system, depending on the conditions of the intoxication. A diagrammatic representation of this proposed mechanism is shown in Diagram 1.

ORGANOLEAD

Organolead, particularly alkylleads, have been widely used in various industries and for agricultural purposes. Despite much investigations have been performed to elucidate the neurotoxicity/neuropathology of inorganic lead, studies on the neuropathological aspects of organolead compounds are relatively few and were recently reviewed by Seawright *et al.* (1984).

TABLE II

CLINICAL SIGNS & SYMPTOMS OF Et₄Pb OR Et₃Pb EXPOSURES

Phase I:	lethargy
Phase II:	inappetance, tremor, hypermotility, hyperexcitability, aggression
Phase III:	hypothermia, convulsion, incoordination, ataxia, paralysis
Phase IV:	death

N.B. : symptoms and signs resemble those observed in trimethyltin, TMT, intoxication.

DIAGRAM I

PROPOSED PATHOGENETIC MECHANISM OF METHYLMERCURY IN CNS

The first comprehensive description on the pathological changes in experimental animals due to the tetraalkyllead compounds (R_4Pb) were made by Davis *et al.* (1963) and Schepers (1964). In these studies, adult rats or dogs were given multiple daily exposures of the compounds by inhalation. The general signs and symptoms of organolead poisoning are summarized in Table II. Levels of lead in the brain at time of death were around $10 \mu/g$. Pathological changes recorded in the brains include various degenerative changes affecting neurons in the neocortex, spinal cord, medulla oblongata, pons, cerebellar cortex, midbrain, thalamus, and basal nuclei. Diffuse neuroglial reactions were also reported. The overall neuropathology of organolead is presented in Table III.

Studies of fine structural changes have been made in the brain of the rabbit after single i.p. doses of Et_3Pb^+ of 1 mg/kg of Et_4Pb

TABLE III

NEUROPATHOLOGY INVOLVEMENT IN ACUTE EXPOSURE
TO Et_4Pb

The neuropathological changes are quite similar to those observed in trimethyltin (TMT) poisoning:

Neuronal necrosis and pyknosis primarily in PYRIFORM/

ENTORHINAL CORTEX, HIPPOCAMPAL FORMATION:
FASCIA DENTATA & AMMON'S HORN, AMYGDALOID
NUCLEI, NEOCORTEX

Neuronal chromatolysis, swelling, and necrosis in the

BRAINSTEM & MIDBRAIN NUCLEI, PONTINE NUCLEI,
BASAL NUCLEI, ANTERIOR CERVICAL SPINAL CORD

In certain species, involvement of cerebellar Purkinji cells are also observed.

(Niklowitz, 1974, 1975) and after multiple i.p. doses of Et_3Pb^+ of 1 mg/kg given every 2nd day for some 30 days (Manthos *et al.*, 1980). Cellular changes were first observed in the nuclei of affected neurons. Nuclear membranes became irregular with condensation and increased osmiophilia of the karyoplasm. These initial changes were followed by hypertrophy of Golgi saccules which, with the marked swelling of some mitochondria and loss of cristae and dilation of endoplasmic reticulum, produced an overall appearance of cytoplasmic vacuolation in some cells. The changes were accompanied by loss of ribosomes from rough endoplasmic reticulum and dispersion of polysomes, a change recognized in the light microscope as chromatolysis.

With rabbits exposed to organolead, Niklowitz (1974) reported that the cytoplasm of some cells become marked by the vacuolar change with little nuclear alteration while other cells show nuclear condensation of the karyoplasm. Niklowitz (1974) also reported that neurofibrils appear plentiful in the cytoplasm of many affected neurons early in the intoxication and mild swelling of astrocytes in regions of altered groups of neurones is usually present.

Study by Sturrock (1979) indicated that a single injection of triethyllead (8 mg/kg) to mice induced a quantitative change in glial population in the brains of these animals. Recent investigations by Chang and co-workers (1984) indicated that both triethyllead (TEL) and trimethyllead (TML) compounds were neurotoxic, inducing alterations in behavioral functions as well as in neuropathological lesions in rats. TEL was found to affect the sensory system of the animals inducing prominent mitochondrial changes (formation of "megamitochondria" or hyper-plasia of "micromitochondria") in the dorsal root ganglion neurons. Accumulations of lysosomes and disintegration of Nissl substance were also observed. TML, on the other hand, induced extensive neuronal changes in the large brain stem neurons and motoneurons in the spinal cord. Neuronal swelling was also observed in the hippocampus after either TEL or TML exposure.

In developmental animals, hypomyelination (underdevelopment of myelin) was observed (Clausen, 1984). This hypomyelination is believed to be the result of inhibition of proteolipid protein (PLP) and intermediate protein (IP) synthesis in the oligodendrocytes (for myelin formation) by alkyllead.

Possible Pathogenetic Mechanism of Alkyllead

Tetraalkyllead (R_4Pb) is not very toxic until it is dealkylated to trialkyllead (R_3Pb) by the hepatic microsomal enzyme. Trialkyllead is

believed to disturb the Cl^- ionic flux and transport of the neurons. Such ionic change would tend to reverse the GABAergic neuron's hyperpolarization action, thus allow the neurons to depolarize with exaggerated excitation (hyperexcitation) which would in turn induce neuronal damage (Cremer, 1984). The increased neuronal excitation will also command increased glucose utilization (Collins *et al.*, 1980) and accumulation of pyruvate and lactic acid, which are highly harmful to neurons. Induction in mitochondrial degeneration and functional deficits will also lower the ATP production which would also lead to neuronal swelling and damage. The formation of "megamitochondria" and hyperplasia of "micromitochondria" probably reflect a compensatory reaction to mitochondrial inefficiencies due to organolead. A general proposed scheme of pathogenetic mechanism of alkyllead is presented in Diagram II.

ORGANOTIN

Although inorganic tin compounds are not known to be particularly neurotoxic, recent investigations have demonstrated that organotin compounds, such as trimethyltin (TMT) and triethyltin (TET), are potent neurotoxins producing rapid and extensive damage to the central nervous system. While TET is known to be primarily myelinotoxic in the central nervous system (Watanabe, 1977, 1980), TMT is found to be extremely neuronotoxic (Brown *et al.*, 1979; Bouldin *et al.*, 1981; Chang, 1984c; Chang *et al.*, 1982a,b,c, 1983a,b; Chang and Dyer, 1983a,b).

Triethyltin (TET)

In 1954, over 200 individuals were intoxicated in France after consuming Stalinon, a proprietary preparation used to treat various infectious ailments. One of the main ingredients of Stalinon capsules were diethyltin diiodide with triethyltin iodide as a major impurity of the preparation. Prominent clinical signs in the patients were nausea, vertigo, visual disturbances, papilledema, apraxia, and convulsions, all suggestive of increased intracranial pressure (Foncin and Gruner, 1979; Gruner, 1958). At autopsy, cerebral edema was pronounced. Subsequent experimental studies confirmed that the major neuropathologic change in TET intoxication was massive cerebral edema, restricted primarily to the white matter (Magee *et al.*, 1957; Torak *et al.*, 1960, 1970). Electron microscopic examination revealed formations of intramyelinic vacuoles (Aleu *et al.*, 1963; Hirano *et al.*, 1968; Graham and Gonatas, 1973; Jacobs *et al.*, 1977). Although the myelinic edema was theoretically "reversible" complete clinical recovery was observed only in approximately 30 % of patients, with symptoms disappearing

DIAGRAM II

POSSIBLE NEUROTOXIC MECHANISM OF TETRAALKYLLEAD

weeks or months after exposure (Foncin and Gruner, 1979) with the remaining patients displaying persistent neurologic damage.

The pathological effects of postnatal TET exposure depend upon the age of the animal and the dosage administered. When triethyltin sulphate (5 mg/kg) was administered to newborn rats, the brains were swollen and petechial hemorrhages were observed in the brain, particularly in the cerebellum (Suzuki, 1971). Necrotic cells were diffusely distributed throughout the CNS. When the same treatment was given to eight-day old animals, in addition to the hemorrhagic and neuronal necrotic changes, myelinated fibers in both brain stem and cerebellum were severely damaged, while the unmyelinated fibers appeared uninvolved (Suzuki, 1971).

Watanabe (1977) also examined the influence of TET on developing brains of mice utilizing light and electron microscopy. Animals were given various doses of TET at different postnatal ages. A definite trend toward longer survival and greater tolerated dose was observed in older animals, suggesting an increased sensitivity in young animals. However, myelinic vacuolation was identified at 24 hours regardless of the animal's age or administered dose. The vacuoles were most frequently observed in the large myelinated fibers, while small myelinated fibers were only slightly involved. However, the myelinic vacuolation resolved rapidly. Ultrastructural examination demonstrated intramyelinic edema, and swelling of both oligodendroglia and astroglia. Massive neuronal necrosis, such as those reported by Suzuki (1971), was not observed, suggesting that while there was an increased myelinic destruction, a reduction of neuronal vulnerability also occurred in older animals.

Padilla and Veronesi (1982) observed transient hypomyelination in young rats given 6 mg TET/kg ip at 5 days of age. Galactocerebroside concentrations (used as a marker for myelin) were reduced to 83% of control values, although this difference disappeared at 2 months of age. The amount of myelin basic protein (MBP) in forebrain myelin, however, was still significantly reduced at both 22 and 60 days. Ultrastructural examination also indicated some remnants of myelin defects even on day 22 of age, but most of these morphological defects resolved in older animals. This hypomyelination effect echoes that seen in organolead poisoning.

Recent study by Veronesi *et al.* (1982) demonstrated that treatment of 5 day old rat pups with 6 to 9 mg TET/kg induced anterior-posterior atrophy of the brains with pronounced cortical thinning. Brains of 22 day old pups showed degenerative neuronal changes, infiltration by

microglia, and increased cellular density in the cortex. Golgi prepared tissues documented dendritic abnormalities of pyramidal cells in layers III and V in later adult specimens. Behavioral work of Harry and Tilson (1981), and Reiter *et al.* (1981) has also revealed persistent behavioral changes in animals given TET on day 5 of life.

Trimethyltin (TMT)

Mice were found to be extremely sensitive to TMT poisoning. Severe whole body tremors and neuronal degeneration, particularly those in the limbic system and brain stem, were observed within 48 hours after single injection of 3.0 mg TMT/kg b.w. (Chang *et al.*, 1982a,b,c, 1983a,b). Degenerative changes in many brain stem neurons were particularly prominent showing extensive chromatolytic and vacuolar changes characterized the pathological alterations in these nerve cells. In the brain stem, the mesencephalic trigeminal nuclei, Locus ceruleus nuclei, and the raphe nuclei were most severely affected. However, scattered neuronal degeneration was also present in other parts of the brain stem. Similar degenerative changes in the larger spinal motoneurons have also been reported (Chang, 1984b). Extensive degeneration of the fasci dentata was also observed in mice treated with TMT.

The overall pathological effects of TMT on rats were much milder than those on mice. Examination of the hippocampus from animals severely treated with 6.0 mg/kg TMT revealed extensive neuronal loss in the Ammon's horn. However, the involvement of fascia dentata was much milder than those observed in mice (Chang *et al.*, 1983b).

Although brain stem lesions also occurred in rats, these lesions were confined to chromatolytic changes only without the extensive vacuolar degeneration as those observed in mice. Extensive pathological lesions in the olfactory tubercle and in the pyriform/entorhinal cortices were also observed (Chang and Dyer, 1983a). Recent study by Chang and co-workers (Chang and Dyer, 1983b) also revealed definitive pathological changes in the Organ of Corti of the inner ear, retina, and dorsal root ganglia of rats exposed to TMT, suggesting a special vulnerability of sensory neurons to TMT toxicity.

Despite the extensive study of TMT neurotoxicity in recent years, most of these investigations were performed on adult animals. Comprehensive studies on the impact of TMT on the developing nervous system were relatively few (Reuhl *et al.*, 1982; Chang, 1984a,b). Among these studies, the most significant observation was perhaps made by Chang and his co-workers (Chang, 1984a,b). These investigators

injected TMT (6.0 mg TMT/kg b.w.) to neonatal rat pups at various neonatal ages and demonstrated selective populations of neurons in the hippocampal formation to be destroyed. As these pathological patterns were well-correlated with the developmental and functional maturity of the hippocampal neurons, these investigators suggested that the production of lesions to the Ammon's horn pyramidal neurons, particularly those in subfield CA₃, required functionally mature and intact granule cells and their fibers (mossy fibers). The concept of "functional toxicity" was first introduced by these investigators to indicate that damage of certain neurons may be the result of adverse alterations of the functional state (e.g. hyperexcitation or hyperstimulation) of these nerve cells under the influence of a chemical (Chang, 1984a,c).

Pathogenetic Mechanism of Trimethyltin on the Hippocampal Formation

The most distinct neuropathology for TMT is in the hippocampal formation. Based on the biochemical data as well as the pattern of pathological lesion development, Chang (1986) proposed that "hyper-

TABLE IV

TMT Effects on Brain Glutamate Metabolism & System

- ↓ glutamate uptake	(Naalsund et al., 1985; Patel et al., 1990)
- ↓ glutamate synthesis	(Patel et al., 1990)
- ↓ GABA synthesis	(Docter et al., 1982; De Haven et al., 1984; Mailman et al., 1985)
- ↑ glutamate release	(Patel et al., 1990)
- ↑ brain tissue glutamine & serum ammonia	(Wilson et al., 1986; Hikal et al., 1988)
- ↑ damage to GABAergic neurons (basket cells)	(Chang and Dyer, 1985)
- ↑ Cl ⁻ flux, reverse GABA's inhibitory (hyperpolarization) effect	(?)

ALL THESE EVENTS WOULD LEAD TO NEURONAL
HYPEREXCITATION

excitation" was the mechanistic base of TMT toxicity in the hippocampal formation.

A disturbance of brain glutamate metabolism and GABAergic system by TMT had been reported by various laboratories (Table IV with references). The reduction in glutamate uptake and synthesis will deplete the neuronal glutamate, which, together with a reduction in brain taurine, probably produced the tremor as seen in the animals. A reduced GABA synthesis was also reported. This reduction of GABA synthesis in the GABAergic neurons (inhibitory), together with an increased release of glutamate under the influence of TMT, will promote the situation of "hyperexcitation". The fact that TMT's toxic impact on the hippocampus

TABLE V

HIPPOCAMPAL CORTICOSTERONE

BINDING: CA_{1,2} > CA₃ > dentate fascia granule neurons
(McEwen et al., 1975)

FUNCTION: inhibition and modulation of neuronal firing rate in
the hippocampus
(Pfaff et al., 1971)

GENERAL VULNERABILITY TO TMT TOXICITY:
d.f. granule neurons > CA₃ > CA_{1,2}
(Chang, 1986)

EFFECT OF ADRENOECTOMY ON TMT TOXICITY:
- adrenoectomized animals show more lesion than intact
animals
- corticosterone supplementation blocks TMT-induced
lesion development
(Chang et al., 1989)

DIAGRAM III

PROPOSED NEUROTOXIC MECHANISM OF TMT ON RAT HIPPOCAMPUS

FIGURE I

LIMBIC PATH vs. TMT-INDUCED LESION DEVELOPMENT

1. Elimination or destruction of entorhinal cortex (rats, 0.8 mg/kg/day, 14 days), spares damage to the entire hippocampal formation (dentate fascia and Ammon's horn).
 2. Elimination or destruction of dentate fascia granule cells (mice, 3.0 mg/kg; rats, ventral hippocampus, 6.0 mg/kg; rats, dorsal hippocampus, 12.5 mg/kg), spares damage to the Ammon's horn neurons.
 3. Elimination or destruction of Ammon's horn CA₃ neurons at the septal portion of the hippocampus (rats, 6.0 mg/kg), spares damage to the CA_{1,2} neurons.
- Sparing of the Ammon's horn CA₃ neurons at the temporal portion of the hippocampus (rats, 6.0 mg/kg), results in damages to the CA_{1,2} neurons.

can either be promoted or alleviated by manipulating the levels of corticosterone (Table V), a known inhibitor of hippocampal activity (Pfaff *et al.*, 1971; McEwen *et al.*, 1975), further support the hyperexcitation hypothesis (Chang *et al.*, 1989).

Chang further suggested that this "chain" of hyperexcitation activity propagates along the limbic circuitry pathway: entorhinal cortex -> dentate fascia granule -> Ammon's horn CA₃ neurons -> Ammon's horn CA_{1,2} neurons (Figure 1). Investigation by Chang and his co-workers tested this hypothesis by elimination of cell populations along this "pathway" and demonstrated that elimination of any given group (e.g. d.f. granule cells) will spare the neuronal groups (e.g. Ammon's horn neurons) at the lower end of the circuitry.

The overall hypothesis for TMT toxicity in the hippocampus is presented in Diagram III.

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