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NEUROTOXICITY OF TRIMETHYLTIN IN HIPPOCAMPUS: A HYPEREXCITATORY TOXICITY

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ABSTRACT: *Trimethyltin (TMT) induced lesions in the rat hippocampal formation was reviewed. Adult rats were treated with a single dose of 6.0 mg TMT/kg b.w. and were sacrificed between 3-60 days following exposure. On the hippocampal formation, the granule cells of fascia dentata showed early changes which subsided considerably at a later time when the destruction of the pyramidal neurons of the Ammon's horn became increasingly pronounced with time, leading to severe destruction of the structure. It is interesting to note that there was an inverse relationship of pathological involvement between the f.d. granule cells and the Ammon's horn neurons; i.e., when there was a large sparing of the granule cells, there was an extensive damage to the Ammon's horn and vice versa. This inverse relationship was also true between the CA_3 neurons and the $CA_{1,2}$ neurons in the Ammon's horn. Progressive zinc loss, as demonstrated by Timm's method, on the Mossy fibers was also observed. Similar Mossy fiber zinc depletion has been demonstrated in electrical stimulatory excitation condition of the perforant path to the hippocampus. Depletion of corticosterone, an inhibitor to the hippocampal neurons, by means of adrenalectomy will exaggerate the TMT induced hippocampal lesion. Neonatal study revealed that a unique degenerative pattern of the Ammon's horn could be established in accordance with exposure to TMT at specific maturation periods of the hippocampal formation: increasing destruction of the Ammon's horn with increasing synaptogenesis between the f.d. granule cells and the Ammon's horn neurons. Thus it is apparent that the damage of the Ammon's horn, upon exposure to TMT, may depend on the integrity and functional state of the f.d. granule cells. A hyperexcitory scheme and mechanism as the toxicity basis of TMT in the hippocampal formation is proposed and discussed.*

Keywords: *Trimethyltin, Neuropathology, Neurotoxic Mechanism, Hyperexcitation*

INTRODUCTION

Organotin compounds have been used as stabilizers of plastic, as chemosterilants, and as fungicides (Smith and Smith, 1975). Recent investigations have demonstrated that organotin compounds, such as trimethyltin (TMT) and triethyltin (TET), are potent neurotoxicants 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 *et al.*, 1982a, b, c; Chang *et al.*, 1983c, 1984; Wenger *et al.*, 1982; Dyer *et al.*, 1982b).

Induction of overt neurological and behavioral changes in rodents, including aggression, hyperirritability, tremor, spontaneous seizures, hyperreactivity, and changes in schedule-controlled behavior by trimethyltin (TMT) compounds are well documented (Brown *et al.*, 1979; Wenger *et al.*, 1982, 1984a, b; Dyer *et al.*, 1982a, c). In rats, such behavioral changes have been referred to as "the trimethyltin syndrome" (Dyer *et al.*, 1982a).

Pathological investigations with rats have demonstrated that the limbic system, particularly the Ammon's horn of the hippocampal formation, is extremely sensitive to the toxicity of TMT (Brown *et al.*, 1979; Chang *et al.*, 1983c, 1985a). It was observed that there was an inverse relationship in lesion development between the entorhinal cortical cells and the dentate fascia (*d.f.*) granule cells, the *d.f.* granule cells and the Ammon's horn CA_3 neurons, as well as the Ammon's horn CA_3 neurons and the $CA_{1,2}$ neurons (Chang and Dyer, 1983b). Investigation with neonatal rats also revealed the dependency of intact, functional *d.f.* granule cells for lesion development in the Ammon's horn (Chang, 1984a, b).

Based on the patterns of the neuropathology development and various neurochemical alterations following TMT exposure, a working hypothesis for the neurotoxic mechanism of trimethyltin in the limbic system is constructed and proposed.

NEUROPATHOLOGY

Mice (adult)

The neuropathology in mice following TMT injection (3.0 mg/kg b.w) was extensively studied by Chang and co-workers (Chang *et al.*, 1982a, b, c, 1984; Wenger, 1982, 1984a, b). Severe tremor was observed in all the animals within 48 hours of TMT injection. Extensive and rapid damage to the *d.f.*,granule cells with little or no observable pathology in the Ammon's horn was found (Chang *et al.*, 1982a, b, c). While there were marked neuronal changes in the brain stem neurons (Chang *et al.*, 1983b), little change was reported in the entorhinal cortex (Table I).

Rats (adult)

TMT-induced neuronal destruction occurs in a number of CNS areas (Chang *et al.*, 1983b), but is more prominent in the hippocampal formation and other limbic struc-

Table 1. Comparison of lesion development in mice and in rats

	MICE	RATS
Entorhinal cortex	±	+ +
d.f. granule cells	+ + +	+
Ammon's horn neurons	–	+ + +

tures of both rats and mice (Chang *et al.*, 1983c). While published accounts of TMT toxicity in rats describe high vulnerability of hippocampal pyramidal neurons, the most sensitive pyramidal cell field has not been convincingly established. Brown *et al.*, (1979) described thinning of $CA_{1,2}$ with sparing of $CA_{3a,b}$ but extensive damage to CA_{3c}. Similarly, Valdes *et al.* (1983) have described sparing of $CA_{3a,b}$ in the face of extensive CA_{3c} damage. In contrast, Dyer and co-workers (Dyer *et al.*, 1982a, b) demonstrated prominent destruction of CA_{3a}, CA_{3b} and CA_{3c} in the hippocampal formation with relative sparing of $CA_{1,2}$. Careful review of the literature reveals that those studies showing $CA_{1,2}$ sensitivity and $CA_{3a,b}$ sparing were based mainly upon coronal sections, while those showing $CA_{3a,b}$ sensitivity were based upon sagittal sections (Chang and Dyer, 1985a).

In an attempt to resolve this controversy, Chang and coworkers (1985a) studied the time-course pathological lesion in TMT-treated rat hippocampus by means of step-sectioning technique on both sagittal (longitudinal) and coronal (cross sectional) planes of the brains. Assessment of the septotemporal distribution of TMT-induced neuronal necrosis appears to have resolved the discrepancy between reports claiming that CA_{3a} and CA_{3b} cells are resistant (Brown *et al.*, 1979; Valdes *et al.*, 1983) vs. those describing sensitivity (Dyer *et al.*, 1982a, b). Based on serial sections in coronal and sagittal planes, it is evident that the fascia dentata granule cells were most involved ventrally and dorsolaterally (temporally) while CA_{3a} and CA_{3b} pyramidal cells were most affected dorsomedially (septally) (Chang and Dyer, 1985a). These investigators also noted that CA_{3c} cells were involved throughout the entire extent of the dorsal hippocampus with the septal pole being most severely affected, and $CA_{1,2}$ cells were most affected at mod-septotemporal levels. Since the population of CA_1 cells in the ventral hippocampus (extreme temporal pole) of rats is relatively small and the functional significance of the ventral hippocampus in rats is still obscure, the full toxic impact or damage to these cells becomes difficult to evaluate accurately.

An interesting phenomenon illustrated by these findings is that there seemed to be an inverse relationship between regional lesion severity for the granule cells and for the Ammon's horn pyramidal neurons, particularly those in fields CA_{3a} and CA_{3b}. Portions of the hippocampus which showed extensive granule cell destruction showed little damage to the CA_{3a} and CA_{3b} pyramidal neurons, while areas showing significant damage to these pyramidal neurons had relatively intact granule cells in the corresponding fascia dentata (Table 1). Similar reversed pathological relationsip was also apparent between the CA_3 and $CA_{1,2}$ pyramidal neurons.

This inverse pathological condition between the *d.f.* granule cells and the Ammon's horn CA_3 neurons echoes that observed in mice where upon severe destruction of the *d.f.* granule cells, the Ammon's horn was spared (Chang *et al.*, 1982a, b). Indeed,

upon extensive destruction of the granule cells in rats, by single highdose exposure to TMT (12.5 mg/kg b.w.), there was also no lesion found in the Ammon's horn (Chang, unpublished observations). Furthermore, when severe destruction of the entorhinal cortex in rats was induced by multiple, low-dose exposures to TMT (0.8 mg/kg for 14 days), no lesion was observed either in the *d.f.* granule cells or in the Ammon's horn of the hippocampus (Chang, unpublished observations) (Fig. 1). Thus, there appears to have a dependency of lesion development for the hippocampal formation (dentate fascia and Ammon's horn) on the integrity of the entorhinal cortex; and lesion development on the Ammon's horn pyramidal neurons may depend on the integrity of the *d.f.* granule cells.

Neonatal Rats

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 (Chang, 1984a, b; Reuhl *et al.*, 1983; Reuhl and Cranmer, 1984). Among these studies, the most significant observations were perhaps those made by Chang and his co-workers (Chang *et al.*, 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. The patterns of injury in the hippocampal Ammon's horn were dependent on the neonatal age at which animals were exposed to the toxicant. No lesion was observed in animals exposed to TMT between postnatal day (PND) 1-4. After PDN 5, however, increasing damage in Ammon's horn was observed in animals exposed to the same dose of TMT. The extent of involvement progressed with exposure at later neonatal ages. The general correlation for injection day vs. loci of involvement were: PND 5-6, CA_{3b}; PND 7, $CA_{3a,\ b}$; PND 8-10, entire

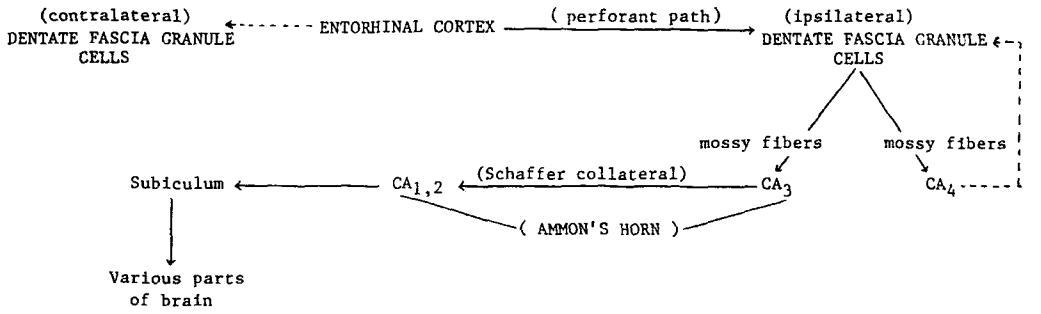

Fig. 1. Limbic path *vs.* TMT-induced lesion development

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 CA_3 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 CA_3 neurons at the temporal portion of the hippocampus (rats, 6.0 mg/kg), results in damages to the $CA_{1,2}$ neurons.

Table 2. Correlation between hippocampal development and TMT-induced lesions in neonatal rats

	PND 1-4	PND 5-6	PND 7	PND 8-10	PND 11-12	PND 13-15
Mossy fiber and synaptic development*	+ (CA_{3b})	+ + (CA_{3b})	+ + ($CA_{3a,b}$)	+ + + ($CA_{3a,b,c}$)	+ + +	+ + + +
Functional efficiency* (Electrical stimulation response)	None	Weak	Stronger response	Responsive but inconsistent	More mature and responsive	Strong and consistent
Damages in Ammon's horn as a result of TMT exposure	None	+ (CA_{3b} only)	+ + ($CA_{3a,b}$)	+ + ($CA_{3a,b,c}$)	+ + + (CA_2, CA_3)	+ + + + ($CA_{1,2,3}$)

*Data interpreted from: Bliss *et al.*, 1974; Stirling and Bliss, 1978; Cowan *et al.*, 1980.

CA_3 ($CA_{3a,\,b,\,c}$); PND 11-12, CA_2 and CA_3; PND 13-15, entire Ammon's horn (CA_1, CA_2, CA_3). The sensitivity of vulnerability of Ammon's horn pyramidal neurons to TMT toxicity, however, became greatly reduced again after PND 20 mimicking those of adult animals. These patterns were very consistent among pups in the same treatment groups and were duplicable with pups from different litters.

It is of interest to note that the distribution of injury observed correlates extremely well with the morphological development and functional maturation of the hippocampal formation in rats, and the functional responsiveness of pyramidal neurons (Bliss, 1974; sterling, 1978; Cowan, 1980). This correlation is summarized in Table 2.

The observations from the neonatal time-course study clearly demonstrated that little or no damage in Ammon's horn could be induced when the mossy fibers were still immature or nonfunctional. Increased lesion development occurs when the development and functional states of mossy fibers (granule cell axons) projecting to Ammon's horn (CA_3) approached maturity (PND) 7-9). Involvement of pyramidal neurons in other fields ($CA_{1,2}$) after PND 10 might indicate the full establishment and functional maturity of the CA_3 pyramidal cell axons (Schaffer collaterals) projecting to and synapsing with pyramidal neurons in $CA_{1,2}$ (Chronister, 1975).

From these data, it becomes apparent that induction of lesions by TMT in the neonatal Ammon's horn was closely associated with and heavily dependent upon the functional maturity and integrity of the neurons and the circuitory in the hippocampal formation. This observation strongly suggests that damages induced in Ammon's horn may not be simply a direct toxicity of TMT on the pyramidal neurons, but, rather, may be the result of altered functional interactions between the granule cells and pyramidal neurons under the influence of TMT. This concept of "functional toxicity" is also supported by observations on the inverse pathological relationship between *d.f.* granule cells and Ammon's horn neurons in adult mice and rats treated with TMT (Table 1).

BIOCHEMICAL FINDINGS

Based on the pathological patterns observed, it appears that the TMT-induced le-

Table 3. 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 amonia	(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

sion development in the limbic system is "neural circutry dependent": entorhinal cortex → *d.f.* granule cells → Ammon's horn CA_3 neurons → Ammon's horn $CA_{1,2}$ neurons (Fig. 1). Such lesion development may also be related to the chain of neural activity and excitability along this neural pathway. Indeed, electroneurophysiology study (Dyer *et al.*, 1982c) demonstrated an reduction of recurrent inhibition (increased excitability) in the dentate gyri after TMT exposure. Pathological survey of these animals further revealed destructions of basket cells (GABAergic neurons) in the dentate fascia within hours of TMT exposure (prior to lesion development in the hippocampal neurons) (Chang and Dyer, 1985b). These observations suggested a disruption of the GABAergic system (inhibitory system) of the hippocampal formation by TMT.

Biochemical studies on the brain of TMT-exposed rats further confirmed that there was a reduction in glutamine and GABA uptake and synthesis (Doctor *et al.*, 1982a, b, c; De Haven *et al.*, 1984; Mailman *et al.*, 1985; Naalsund *et al.*, 1985; Patel *et al.*, 1990). An increased synaptic release of glutamate was also observed (Patel *et al.*, 1990). These events will deplete the interaneuronal glutamate level which, together with a reduction in brain taurine (Hikal *et al.*, 1988), may be responsible for the tremors observed in the TMT-treated animals. The excessive neuronal release of glutamate (Patel *et al.*, 1990) may be responsible for the elevations of brain tissue glutamine (breakdown product of glutamate) (Hikal *et al.*, 1988) and serum ammonia (breakdown product of glutamine) in TMT-treated animals (Wilson *et al.*, 1986; Hikal *et al.*, 1988).

The alterations on glutamate and GABAergic system as a result of TMT exposure is summarized in Table 3.

PROPOSED NEUROTOXIC MECHANISM OF TMT ON HIPPOCAMPUS

Based on the toxicopathological patterns induced by TMT in the limbic system of adult and neonatal animals, a working hypothesis on the neurotoxic mechanism of TMT on the hippocampus may be proposed.

When one compares the pathological patterns of TMT on the hippocampal formation, there seemed to be a different pathological pattern of involvement in the septal and temporal portions of the rat hippocampus: while the temporal portions of the hippocampus showed more granule cell damage and little CA_3 pyramidal cell changes, the septal portion of the hippocampus showed more extensive destruction of the CA_3 pyramidal neurons with comparatively less involvement of the granule cells. The inverse pathological pattern between the fascia dentata granule cells and the CA_3 pyramidal neurons of the Ammon's horn suggested that the functional relationship between these two cell types may play an important role in the pathogenesis of TMT toxicity in the hippocampal formation. That is, the extent of damage to the CA_3 cells may be a function of the density of input from intact granule cells of the fascia dentata. Thus, the absence or reduction of granule cells (cell loss) might reduce or spare some of the Ammon's horn neurons from damages. Coupled to this hypothesis is the observation that the density of mossy fiber innervations of CA_3 cells decreases as one proceeds more temporally (Gaarskjaer, 1978a), potentially accounting for the septotemporal gradient of $CA_{3a,b}$ damage. The invariably more extensive damage to CA_{3c} than $CA_{3a,b}$ may reflect the heavier input of mossy fibers to these neurons (Gaarskjaer, 1978b), particularly including the input from the infrapyramidal bundle (Haug, 1974).

Data generated from the neonatal studies (Chang, 1984a, b) also support the concept that the destruction of Ammon's horn pyramidal neurons required the developmental maturity of the mossy fibers (axons of the granule cells) which project from fascia dentata to the CA_3 pyramidal neurons of the Ammon's horn. These findings strongly suggest that the functional status of the granule cells and their fibers (mossy fibers) play an important role in the inducton of neuronal damage in the CA_3 pyramidal cells of the Ammon's horn.

The concept of "hyperexcitation" of the fascia dentata granule cells in the induction of CA_3 neuron necrosis have actually been demonstrated by other means rather than by TMT: such as by sustained electrical stimulation of the perforant path (Sloviter, 1981a) or by kainic acid administration(Sloviter, 1981b).

It has been demonstrated that heightened synaptic activation of granule cells can produce necrosis in the CA_3 target neurons of the granule cell axons (sloviter, 1981a). Such hyperactivation has been postulated as a mechanism of both kainic acid-induced (Sloviter, 1981b) and TMT-induced (Chang, 1986) CA_3 degeneration. Indeed, granule cell destruction prevents kainic acid-induced CA_3 degeneration (Nadler and Cuthbertson, 1980). Other investigators have also shown that TMT or Kainic acid-induced CA_3 damage in mice or rats can be prevented by eliminating the granule cells (Chang *et al.*, 1982a, b; Nadler and Cuthbertson, 1980; Nadler, 1981).

There is also indirect evidence that TMT induces hyperactivation of the dentate granule cells. It was found that TMT reduced recurrent inhibition in the dentate gyrus, which would increase granule cell activity (Dyer *et al.*, 1982c). It has been shown that both sustained electrical stimulation of the entorhinal cortex (perforant path) input to the granule cells (Sloviter, 1984) and TMT administration (Chang and Dyer, 1984) produced a similar change in the dentate gyrus-a loss of hippocampal and mossy fiber zinc contents. Zimmer *et al.* (1982) have also shown that stimulation of the prepyriform cortex produced, via a dysynaptic route, a response in the granule cells which

was greatly potentiated following TMT. Monosynaptic activation of the granule cells, however, did not seem to produce this potentiation, thereby suggesting that the change was probably not in the granule cells themselves, but rather in the way in which they were activated.

Elimination of corticosterone to the hippocampal formation by adrenalectomy was found to exaggerate lesion development in the hippocampal formation by TMT, and supplementation of this hormone served to reduce or alleviate lesion this development (Chang *et al.*, 1989). Since corticosterone is rich in the hippocampal formation (McEwen *et al.*, 1975) and is believed to inhibit or modulate the neuronal firing rate (excitation) in the hippocampus (Pfaff *et al.*, 1971), this observation further supports the "hyperexcitation" theory as proposed. The TMT toxicity relationship with hippocampal corticosterone is summarized in Table 4.

Biochemical data have also lent support to this general concept of hyperexcitation of the granule cells. Works by Doctor and co-workers demonstrated TMT inhibits the uptake of GABA by synaptosomes both *in vivo* and *in vitro* (Doctor *et al.*, 1982c). These investigators suggested that a blockade of GABA uptake, at least initially, could lead to a prolongation of the postsynaptic inhibitory action of released GABA. However, a long-term sustained increase in the extracellular concentration of GABA due to a sustained inhibition of uptake, as observed with TMT, may lead to a depletion of GABA in presynaptic vesicles as well as impair the efficiency of the recurrent inhibitory system (Doctor *et al.*, 1982a, b, c; 1983). Dose-dependent alterations in the uptake of endogenous glutamic acid and GABA have also recently been reported in synaptosomes isolated from mature rat hippocampus (Valdes, 1983). These investigators suggested that damage to GABA-utilizing basket cells led to decreased inhibition to the recurrent loop involving dentate granule cells. Indeed, by means of electro-physiology, Dyer and co-workers demonstrated a rapid (within hours) reduction of recurrent inhibition in the granule cells following TMT administration and proposed a reduction of basket cell inhibition in the dentate gyrus (Dyer *et al.*, 1982c). Furthermore, electron microscopic investigation of rats intoxicated with TMT also revealed morpake and 32X and degenerative changes in the dentate basket cells Thesely as 24 hours after TMT administration (Chang and Dyer, 1985b). Recent works by Patel and co-workers (1990)

Table 4. Hippocampal corticosterone

BINDING	: $CA_{1,2}$ > CA_3 > 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 > CA_3 > $CA_{1,2}$ (Chang, 1986)
EFFECTS OF ADRENOECTOMY ON TMT TOXICITY:	— adrenoectomized animals show more lesion than intact animals — corticosterone supplementation blocks TMT-induced lesion development (Chang *et al.*, 1989)

also demonstrated and confirmed a reduction in glutamate uptake and synthesis by neurons under the influence of TMT. These investigators further showed an increased glutamate release by neurons under the exposure to TMT. This increased glutamate release may well explain the elevated brain tissue glutamine (breakdown product of glutamate) and serum ammonia (breakdown product of glutamine) in animals exposed to TMT (Wilson *et al.*, 1986; Hikal *et al.*, 1988).

In sum, there is ample evidence from both neuropathological, neurophysiological, and neurochemical investigations to indicate that TMT may act on the inhibitory systems (GABA metabolism, and inhibitory basket cells and/or other interneurons) of the hippocampus to stage an hyperexcitory state of the dentate granule cells and to produce hyperstimulatory damage to their target cells (Ammon's horn pyramidal neurons).

Other cellular events such as increased Cl^- ion flux and seen in organolead exposure (Cremer, 1984) may also occur. The flux of Cl^- ion would further reverse the GABA inhibitory effect. The hyperexcitation of hippocampal neurons would also tend to deplete extracellular Ca^{++} and hippocampal Zn^{++} and corticosterone which may in turn promote more neuronal activity. Thus, a vicious cycle of hyperactivity may be set up (Fig. 2). Neuronal injury may be derived from exhaustion of neuronal ATP, from increased lactic acid accumulation as a result of increased glucose utilization and glycolysis and/or from direct over-depolarization of the neurons under continuous, high potential excitation. The general proposed toxic mechanism for TMT is summarized in Fig. 2.

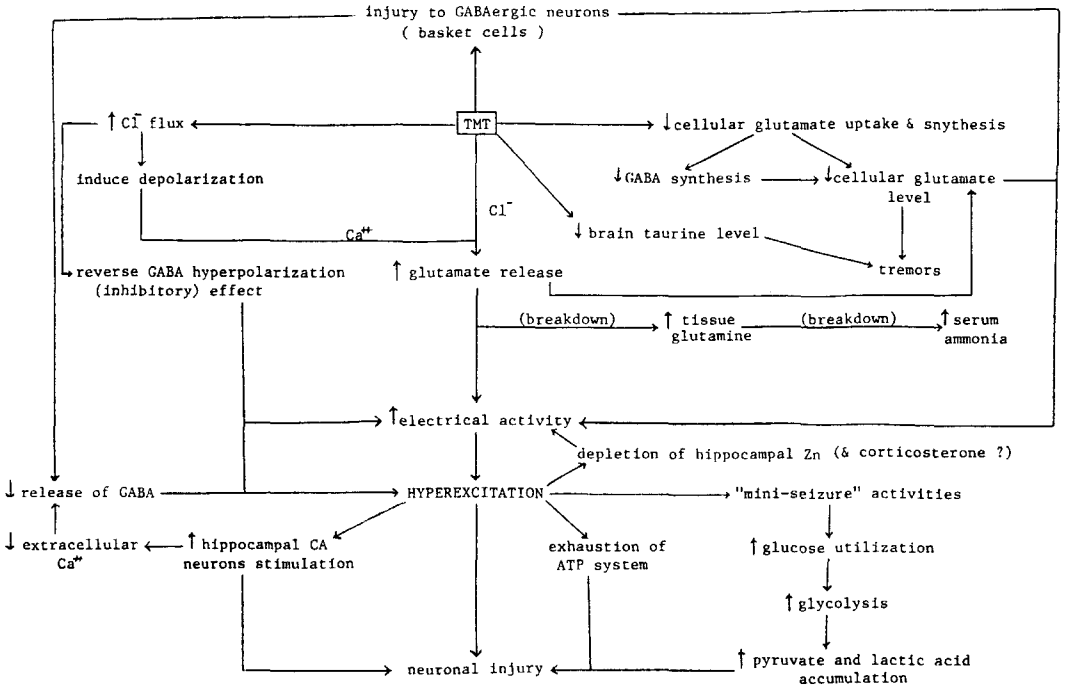

Fig. 2. Proposed neurotoxic mechanism of TMT on rat hippocampus

It must be emphasized that our present proposal only represents a postulation and a working hypothesis. It helps to explain most, though not all, of the pathological patterns in the limbic system in mouse and in rat as a result of TMT intoxication. Needless to say, direct toxicity of TMT on the neurons certainly exists (such as those in the brain stem and spinal cord). Based on the rapid and early cellular edematous change observed on many neurons following TMT exposure (Chang *et al.*, 1982a, b; 1983a, b; 1984), one would suspect a direct disturbance of the neuronal ATP system by TMT may also occur.

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REFERENCES

Bliss, T.V.P., Chung, S.H., and Stirling, R.V. (1974): Structural and functional development of the mossy fiber system in the hippocampus of the postnatal rat, *J. Physiol.* **239,** 92-96.

Bouldin, T.W., Goines, N.D., Bagnell, C.R., and Krigman, M.R. (1981): Pathogenesis of trimethyltin neuronal activity, ultrastructural and cytochemical observations, *Am. J. Pathol.*, **104,** 237-249.

Brown, A.W., Aldridge, W.N., Street, B.W., and Verschoyle, R.D. (1979): The behavioral and neuropathologic sequelae of intoxication by trimethyltin compounds in the rat, *Am. J. Pathol.*, **97,** 59-81.

Chang, L.W. (1984a): Hippocampal lesions induced by TMT in the neonatal rat brain, *Neurotoxicology* **5**(2), 205-216.

Chang, L.W. (1984b): Trimethyltin induced hippocampal lesions at various neonatal ages, *Bull. Environ. Contam. Toxicol.*, **33,** 295-301.

Chang, L.W. (1986): Neuropathology of trimethyltin-a proposed pathogenetic mechanism, *Toxicol. Appl. Pharmacol.*, **6,** 217-232.

Chang, L.W., and Dyer, R.S. (1983a): Effects of trimethyltin on sensory neurons. *in Disease and Chemically Induced Neuro logical Dysfunction, Neurobehav. Toxicol. Teratol.*, **5,** 673-696.

Chang, L.W., and Dyer, R.S. (1983b): A time-course study of trimethyltin-induced neuropathology in rats, *Neurobehav. Toxicol. Teratol.*, **5,** 443-459.

Chang, L.W., and Dyer, R.S. (1984): Trimethyltin-induced zinc depletion in rat hippocampus, *in Neurobiology of Zinc.* (C. Frederickson and G. Howell, Eds.), Alan R. Liss, Inc., pp. 275-290.

Chang, L.W., and Dyer, R.S. (1985a): Septotemporal gradients of trimethyltin-induced hippocampal lesions, *Neurobehav. Toxicol. Teratol.*, **7,** 43-49.

Chang, L.W., and Dyer, R.S. (1985b): Early effects of trimethyltin in the dentate gyrus basket cells: a morphological study, *J. Toxicol. Environ. Health*, **16,** 641-653.

Chang, L.W., Hough, A.J., Bivens, F., and Cockerill, D. (1989): Effects of adrenalectomy and corticosterone on hippocampal lesions induced by trimethyltin, *Biomedical Environ. Sci. Res.*, **2,** 54-64.

Chang, L.W., McMillan, D.E., Wenger, G.R., and Dyer, R.S. (1983a): Comparative studies of the neuropathological effects of trimethyltin in mice and rats, *Toxicologist*, **3**(1), 76.

Chang, L.W., Tiemeyer, T.M., Wenger, G.R., and McMillan, D.E. (1982a): Neuropathology of mouse hippocampus in acute trimethyltin intoxication, *Neurobehav. Toxicol. Teratol.*, **4,** 149-156.

Chang, L.W., Tiemeyer, T.M., Wenger, G.R., McMillan, D.E., and Reuhl, K.R. (1982b): Neuropathology of trimethyltin intoxication. I. Light microscopy study, *Environ. Res.*, **29,** 435-444.

Chang, L.W., Tiemeyer, T.M., Wenger, G.R., McMillan, D.E., and Reuhl, K.R. (1982c): Neuropathology of trimethyltin intoxication. II. Electron microscopy study of the hippocampus, *Environ. Res.*, **29,** 445-458.

Chang, L.W., Tiemeyer, T.M., Wenger, G.R., and McMillan, D.E. (1983): Neuropathology of trimethyltin intoxication. III. Changes in the brain stem neurons, *Environ. Res.*, **30,** 399-411.

Chang, L.W., Wenger, G.R., and McMillan, D.E. (1984): Neuropathology of trimethyltin intoxication, IV. Changes in the spinal cord, *Environ. Res.*, **34,** 123-134.

Chang, L.W., Wenger, G.R., McMillan, D.E., and Dyer, R.S. (1983c): Species and strain comparison of acute neurotoxic effects of trimethyltin in mice and rats, *Neurobehav. Toxicol. Teratol.*, **5,** 337-350.

Chronister, R.B., and White, L.E. (1975): Fiberarchitecture of the hippocampal formation; Anatomy, projections, and structural significance, *in The Hippocampus*, Vol. I. (R.L. Isaacson and K.H. Primbram Eds.). Plenum Press, New York, p. 9-18.

Costa, L.G., Doctor, S.V., and Murphy, S.D. (1982): Antinociceptive and hypothermic effects of trimethyltin, *Life Sci.*, **31,** 1093-1102.

Cowan, W.M., Stanfield, B.B., and Sishi, K. (1980): The development of the dentate gyrus, *in Current Topics in Developmental Biology*, Vol. 15 (R.K. Hung Ed.), Academic Press, New York, p. 103-115.

Cremer, J.E. (1984): Possible mechanism for the selective neurotoxicity. *in Biological Effects of Organolead Compounds* (P. Grandjean Ed.). CRC press, N.Y., p. 145-160.

De Haven, D.L., Walsh, T.J., and Mailman, R.B. (1984): Effects of TMT on dopaminergic and serotonergic functions in the CNS, *Toxicol. Appl. Pharmacol.*, **74,**

182-289.

Doctor, S.V., Costa, L.G., Kendall, D.A., Enna, S.J., and Murphy, S.D. (1982a): Studies on the neurotoxicity of trimethyltin, *Toxicologist*, **2,** 86.

Doctor, S.V., Costa, L.G., Kendall, D.A., and Murphy, S.D. (1982b): Trimethyltin in hibits uptake of neurotransmitters into mouse forebrain synaptocomes, *Toxicology*, **25,** 213-223.

Doctor, S.V., Costa, L.G., and Murphy, S.D (1982c): Effect of trimethyltin on chemically-induced seizures, *Toxicol. Lett.*, **13,** 217-223.

Doctor, S.V., Costa, L.G., Kendall, D.A., and Murphy, S.D. (1982b): Trimethyltin in various tissues of the male mouse, *Toxicol. Lett.*, **17,** 43-48.

Dyer, R.S. (1982): Physiological methods for assessment of trimethyltin toxicity, *Neurobehav. Toxicol. Teratol.*, **4,** 659-665.

Dyer, R.S., Walsh, T.J., Wonderlin, W.F., and Bercegeay, M. (1982a): The trimethyltin syndrome in rats, *Neurobehav. Toxicol. Teratol.*, **4,** 127-133.

Dyer, R.S., Wonderlin, W.F., and Deshields, T.L. (1982b): Trimethyltin-induced changes in gross morphology of the hippocampus, *Neurobehav. Toxicol. Teratol.*, **4,** 141-147.

Dyer, R.S., Walsh, T.J., Swartzwelder, H.S., and Wayner, M.J. (eds) (1982c): Neurotoxicology of the alkyltins, *Neurobehav. Toxicol. Teratol.*, **4**(2) (special issue).

Dyer, R.S., Wonderlin, W.F., Walsh, T.J., and Boyes, W.K. (1982c) Trimethyltin reduces basket cell inhibition in the dentate gyrus, *Soc. for Neurosci. Abst.*, **8** (No 23.7), 82.

Gaarskjaer, F.B. (1978a): Organization of the mossy fiber system of the rat studied in extended hippocampi. II. Experimental analysis of fiber distribution with silver impregnation methods, *J. Comp. Neurol.*, **178,** 73-81.

Gaarskjaer, F.B. (1978b): Organization of the mossy fiber system of the rat studied in extended hippocampi. I. Terminal area related to number of granule and pyramidal cells, *J. Comp. Neurol.*, **178,** 49-56.

Haug, F. -M.S. (1974): Light microscopical mapping of the hippocampal region, the pyriform cortex and the corticomedial amygdaloid nuclei of the rat with Timm's sulfide silver method, *Z. Anat. Entwickl.* -Gesch., **145,** 1-7.

Hikal, A.H., Light, G.W., Shikker, W., Scarlet, A., and Ali, A.F. (1988): Determination of amino acid in different regions of rat brain application to acute effects of TMT, *Life Sci.*, **42,** 2029-2035.

Mailman, R.B., Krigman, M.R., Frye, G.D., and Hannin, Z. (1983): Effects of postnasal trimethyltin or triethyltin treatment of CNS catecholamines, GABA, and acetyl choline systems in the rat, *J. Neurochem.*, **40,** 1423-1429.

McEwen, B.S., Gerlach, J.L., and Micco, D.J. (1975). Putative glucocorticoid receptors in hippocampus and other regions of the rat brain. *in The hippocampus*, Vol. I (R.L. Isaacson and K.H. Pribram Ed.), p. 285-322.

Naalsund, L.V., Suen, C.N., and Fonnum, F. (1985): Changes in neurobiological parameters in the hippocampus after exposure to TMT, *Neurotoxicology*, **6,** 145-158.

Nadler, J.V. (1981): Kainic acid as a tool for the study of temporal lobe epilepsy-minireview, *Life Sci.*, **29,** 2031-2042.

Nadler, J.V., and Cuthbertson, G.J. (1980): Kainic acid neurotoxicity toward hippocampal formation: dependence on specific excitatory pathways. *Brain Res.*, **195,** 47-56.

Patel, M., Ardelt, B.K., Yim, G.K.W., and Isom, G.E. (1990): Interaction of trimethyltin with hippocampal glutamate, *Neurotoxicology, (in press).*

Reuhl, K.R., and Cranmer, J.M. (1984): Developmental neuropathology of organotin compounds, *Neurotoxicology,* **5**(2), 187-195.

Reuhl, K.R., Smallridge, E.A., Chang, L.W., and Mackenzie, B.A. (1983). Developmental effects of trimethyltin intoxication in the neonatal mouse I. Light microscopic studies, *Neurotoxicology,* **4**(1), 19-28.

Sloviter, R.S. (1984). A selective loss of Timm staining in the hippocampal mossy fiber pathway accompanies electrically induced hippocampal granule cell seizure activity in rats. *in Neurobiology of Zinc,* (C.J. Frederickson and G.A. Howell. (Eds.)) Alan R. Liss, Inc., New York, p. 127-138.

Sloviter, R.S., and Damiano, B.P. (1981a): Sustained electrical stimulation of the perforant path duplicates kainate-induced electrophysiological effects and hippocampal damage in rats, *Neurosci. Lett.*, **24,** 279-284.

Sloviter, R.S., and Damiano, B.P. (1981b): On the relationship between kainic acid-induced epileptiform activity and hippocampal neuronal damage, *Neuropharmacology,* **20,** 1003-1011.

Smith, P., and Smith, L (1975): Organotin compounds and applications, *Chem. Br.*, **11,** 208-226.

Stirling, R.V., and Bliss, T.V.P. (1978): Hippocampal mossy fiber development at the ultrastructural level, *Prog. Brain Res.*, **48,** 191-206.

Valdes, J.J., Mactutus, C.F., Santos-Anderson, R.M., Dawson, R., Jr., and Annu, Z. (1983): Selective neurochemical and histological lesions in rat hippocampus following chronic trimethyltin exposure, *Neurobehav. Toxicol. Teratol.*, **5,** 357-361.

Watanabe, I. (1977): Effect of triethyltin on the developing brain of the mouse *in Neurotoxicology.* L. Roizin, H. Shiraki, and N. Grcevic (Eds.). Raven Press, New York p. 317-326.

Watanabe, I. (1980). Organotins. *in Experimental and Clinical Neurotoxicology.*, P.S. Spencer and H.H. Schaumburg.(Eds.)), Williams and Wilkins, Baltimore, p. 545-557.

Wenger, G.R., McMillan, D.E., and Chang, L.W. (1982): Behavioral toxicology of acute trimethyltin exposure in the mouse, *Neurobehav. Toxicol. Teratol.*, **4,** 157-161.

Wenger, G.R., McMillan, D.E., and Chang, L.W. (1984a): Behavioral effects of trimethyltin in two strains of mice. I. Spontaneous motor activity, *Toxicol. Appl. Pharmacol.*, **73,** 78-88.

Wenger, G.R., McMillan, D.E., and Chang, L.W. (1984b): Behavioral effects of trimethyltin in two strains of mice. II. Multiple fixed-ratio, fixed-interval, *Toxicol. Appl. Pharmacol.*, **73,** 89-96.

Wilson, W.E., Hudson, B.M., Kanamatsu, D., Kanamatsu, D., Walsh, T., Tilson, H.,

and Hong, J. (1986): TMT-induced alterations in brain amino acid, amines, and amine metabolites: relationship to hyperammoniemia, *Neurotoxicology*, **7**, 63-74.

Zimmer, L., Hasan, Z., Woolley, D., and Chang, L.W. (1982): Evoked potentials in the limbic system of the rat reveal sites of trimethyltin toxicity, *Neurotoxicology* **3**(3), 135-136.