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Trimethyltin-induced loss of NMDA and kainate receptors in the rat brain

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Summary. Adult rats exposed acutely to trimethyltin (TMT) manifest a number of behavioral alterations, in conjunction with neuronal degeneration in the limbic system. In the present study, changes in ^{3}H-TCP binding to N-methyl-D-aspartate (NMDA) receptors and ^{3}H-kainic acid (KA) binding to kainate receptors were studied by autoradiographic methods following TMT exposure (8 mg/kg, i.p.) in adult Sprague Dawley rats. No significant alterations were found at 4 hours after exposure. An extensive loss of ^{3}H-TCP and ^{3}H-KA binding was seen in the hilar region of the CA3 field at 2 and 12 weeks after TMT exposure. Also, the ^{3}H-TCP binding was decreased in piriform cortex and in striatum. Thus, TMT exposure leads to a major and regional selective loss of NMDA and kainate receptors in the limbic system, alterations that may be involved in the neuropathology and behavioral sequelae of TMT toxicity.

Keywords: Amino acids – Trimethyltin – Glutamate system – NMDA receptors – Kainate receptors – Hippocampus

Abbreviations: TMT: trimethyltin; NMDA: N-methyl-D-aspartate; KA: Kainic acid; TCP: N-(1-2-thienylcyclohexyl)-3,4-piperidine

Introduction

Organotin compounds have widespread industrial and agricultural applications; for example, lower molecular weight trialkyltins are used as stabilizers of plastics, as chemosterilants and as biocides (Piver, 1973). Accidental exposure to the alkyltin trimethyltin (TMT) in man has been reported to cause anorexia, mental confusion, rage reactions, epileptic seizures and depression as well as memory loss (Fortemps et al., 1978; Ross et al., 1981). In adult rats, acute TMT intoxication produces a behavioral syndrome, which in the early period after

exposure includes aggression (Brown et al., 1979), hyperirritability, tremor and convulsive episodes (Dyer et al., 1982). Locomotor hyperactivity has been shown to develop several days after TMT exposure. In addition, a number of deficits in cognitive tasks have been found to occur following TMT exposure. Thus, an impairment in learning and memory has been demonstrated in the radial maze (Walsh et al., 1982), in the Hebb-Williams maze (Swartzwelder et al., 1982), in the Morris maze and in passive avoidance behavior (Earley et al., 1990; Hagan et al., 1988). A hallmark of TMT neurotoxicity in rats is a loss of neurons in the hippocampal CA3 field of Ammon's horn, although other limbic regions may be affected as well, e.g. the amygdaloid nuclei, the piriform/entorhinal cortex as well as pyramidal cells in the neocortex (Bouldin et al., 1981; Brock and O'Callaghan, 1986; Brown et al., 1979; Chang and Dyer, 1983; Woodruff and Baisden, 1990). The neurotoxic mechanisms of TMT are not well understood, although it has been suggested that damage of neurons occur due to hyperstimulation, possibly through dysfunction in the regulation of excitatory amino acid neurotransmission in the brain (Chang, 1986).

In the present study we have investigated the effects of a single dose of TMT on NMDA and kainate receptors over time in adult rats. The receptor binding was determined in brain sections by *in vitro* autoradiographic techniques using ^{3}H-TCP and ^{3}H-KA as ligands.

Materials and methods

Animals and treatment

Male adult Sprague-Dawley rats (approx. 200 g; B&K Universal AB, Sollentuna, Sweden) were housed in air-conditioned rooms with constant temperature and a standardized light/dark schedule (12/12 h; light on at 06.00 h and off at 18.00 h). Food and water were supplied *ad libitum*. Trimethyltin chloride (TMT, Heraeus) was injected intraperitoneally (i.p.) in a dose of 8 mg/kg body weight. The animals were sacrificed at 4h, 2 and 12 weeks after TMT administration by decapitation. The brains were rapidly removed and frozen on dry ice and stored at $-70°$ C until sectioning. The brains were cut in a cryostat (Leitz, Germany) at $-15°$ C in 14 μm frontal sections from the dorsal hippocampus and hippocampus/mesencephalon, levels 30 and 37 according to the rat brain atlas of Swanson (Swanson, 1992). The sections were collected on gelatin coated glass slides and stored at $-70°$C, until the autoradiographic experiments were performed. Sections from paraformaldehyde-perfused animals were also obtained and stained with cresyl violet.

^{3}H-TCP and ^{3}H-KA in vitro autoradiography

The sections were dried in room temperature for at least 120 min before preincubation. TCP autoradiography was performed according to Maragos et al. (1986). The sections were preincubated for 30 min at 4°C in Tris-acetate buffer (50 mM, pH = 7.4) including 4 mM $CaCl_2$. The sections were dried again followed by an incubation at room temperature for 45 min in the Tris-acetate buffer containing 1 mM magnesium acetate and 20 nM ^{3}H-TCP in the presence or absence of 20 μM phencyclidine (PCP) to define non-specific binding. The incubation was terminated by washing the sections in ice-cold Tris-acetate buffer for 3 × 1 min. The sections were then dried under a stream of cool air and subsequently apposed to ^{3}H-sensitive film (Amersham, England) and stored at $-20°$C in X ray cassettes for 8 weeks.

KA autoradiography was performed according to Patel et al. (1986). The sections were preincubated for 15 min at 30°C in Tris-acetate buffer (50 mM, pH = 7.2). The sections were

then incubated at 4°C for 120 min in the Tris-acetate buffer containing 12.5 nM ^{3}H-KA in the presence or absence of 100 μM KA to define non-specific binding. The incubation was

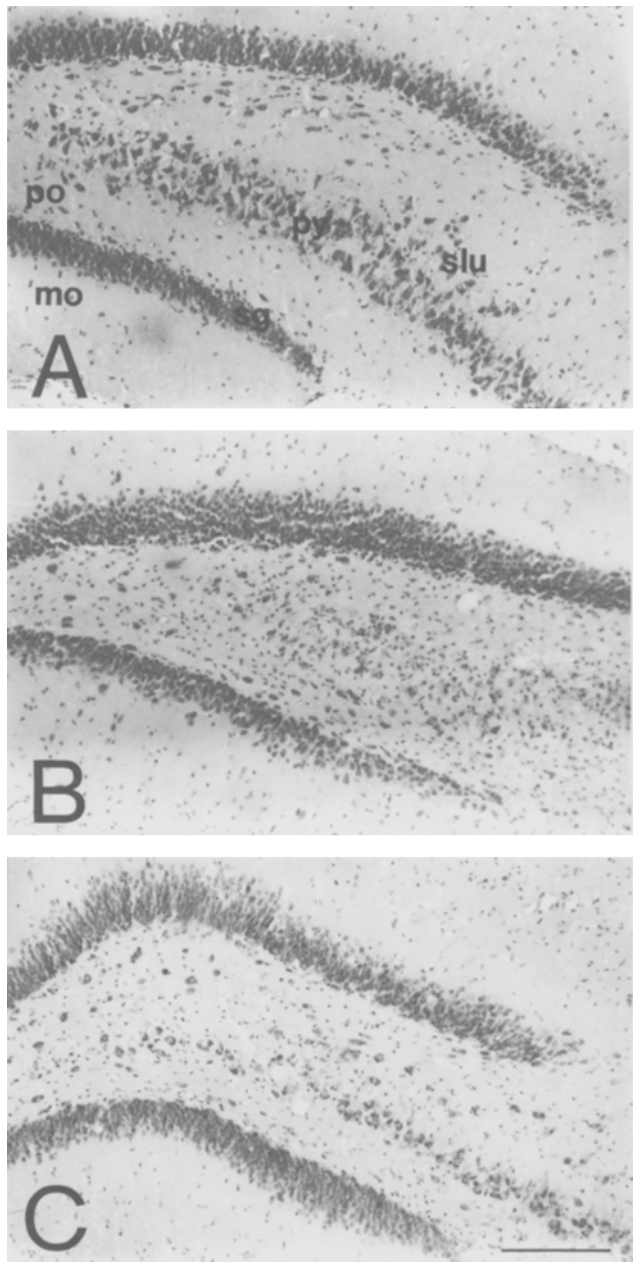
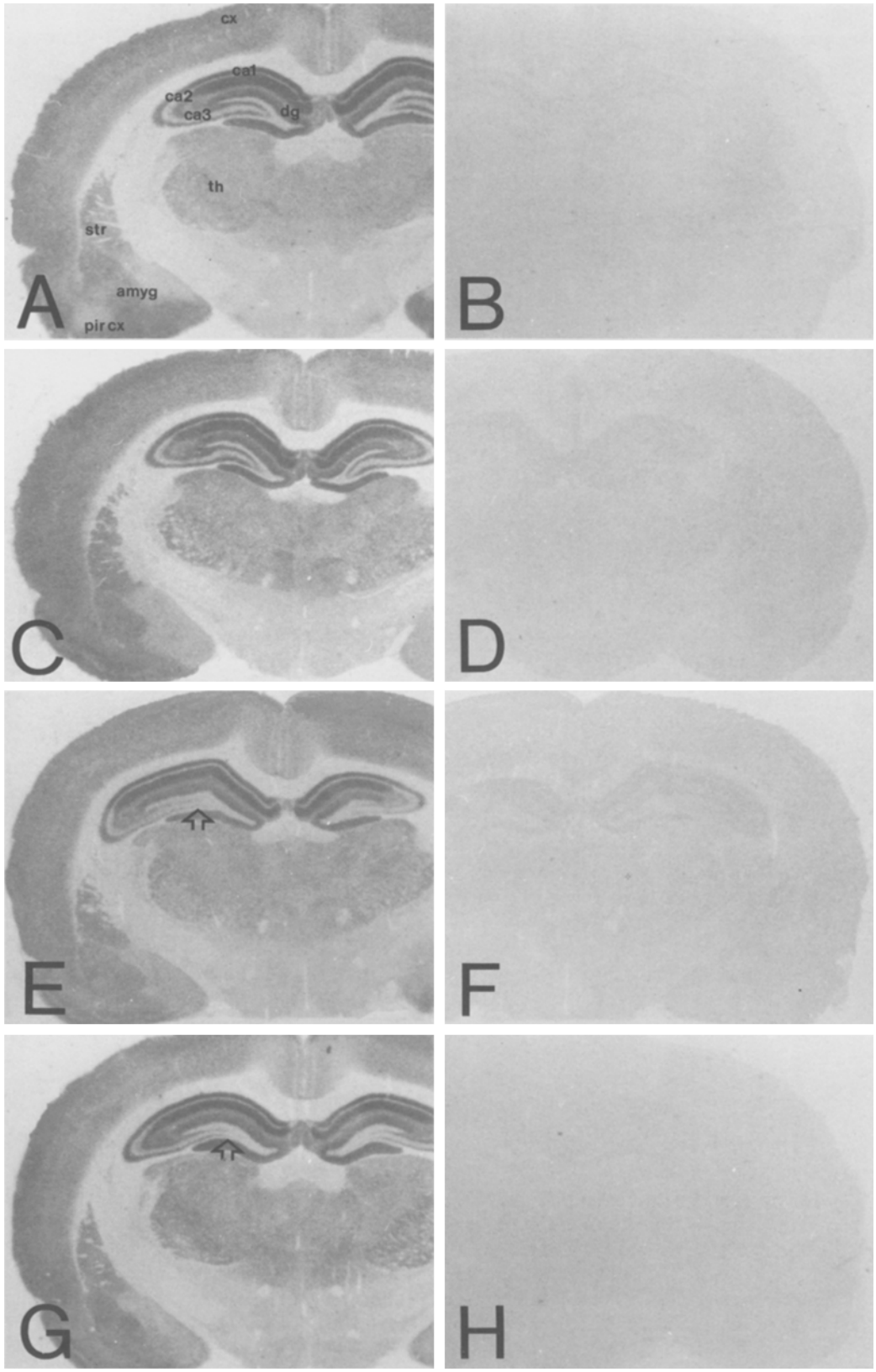


Fig. 1. Micrographs of the dentate gyrus and CA3c field of Ammon's horn in Nissl stained frontal sections of the dorsal hippocampus of the rat brain. **A** Section of a control rat. **B** Section of a rat treated with TMT 2 weeks earlier. **C** Section of a rat treated with TMT 12 weeks earlier. Note the apparent loss of neurons in the pyramidal layer of the CA3c region at 2 and 12 weeks after TMT treatment. *mo* molecular layer of the dentate gyrus; *sg* granule cell layer of the dentate gyrus; *po* polymorph layer of the dentate gyrus; *py* pyramidal layer of the CA3c field of Ammon's horn; *slu* stratum lucidum of the CA3c field of Ammon's horn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terminated by washing the sections in ice-cold buffer for 15 sec, followed by a 3 ml rinse in ice-cold glutaraldehyde-acetone solution, diluted 1:19. The sections were rapidly dried under a stream of warm air and subsequently apposed to ^{3}H-sensitive film (Amersham, England) and stored at −20°C in X-ray cassettes for 8 weeks.

Analysis of the autoradiographs were performed by quantitative microdensitometry using an IBAS Kontron image analysis system (IBAS 200; Zeiss/Kontron, Germany) which converted the density in the film to estimated tissue equivalent binding in fmol/mg tissue (wet weight) by the use of calibrated ^{3}H-plastic standards (Amersham, England) co-exposed with the tissue sections.

Compounds

Tritiated TCP (Lot no: 2890-077) was purchased from NEN, specific activity 50.4 Ci/mmol, in a concentration of 1 mCi/ml. PCP was synthesized at Astra Arcus AB (Batch: OA 748/19). Tritiated KA (Lot no: 2924-012) was purchased from NEN, specific activity 58.0 Ci/mmol, in a concentration of 1 mCi/ml. Unlabeled KA (Lot no: 60H0195) was purchased from Sigma Chemical Company.

Results

Cresyl violet histology

The TMT treatment produced morphological alterations of the pyramidal neurons in the CA3 region of hippocampus, as visualized using cresyl violet staining (Fig.1). No apparent morphological changes were seen at 4h after TMT administration. At two weeks after TMT treatment, an extensive loss of CA3 pyramidal neurons was observed, concomitant with a massive increase in glial cell nuclei (Fig.1B). At 12 weeks after TMT administration, the cell number in the CA3 pyramidal layer was still reduced, especially in the hilar region (Fig.1C). Minor cell losses were also observed in the piriform/entorhinal cortex in the TMT treated rats. The neocortex was only slightly, or not at all, affected by the TMT treatment.

^{3}H-TCP receptor autoradiography

A regionally selective binding of ^{3}H-TCP was seen in the autoradiographs, which could be displaced to a major extent (80–90%) with PCP (Fig. 2). The

Fig. 2. Autoradiographs of *in vitro* binding of ^{3}H-TCP to NMDA receptors in frontal sections of the dorsal hippocampus of the rat brain (**A, C, E** and **G**) and autoradiographs of sections incubated with ^{3}H-TCP in the presence of 20 μM PCP to define non-specific binding (**B, D, F** and **H**). **A** and **B** Autoradiographs of sections from a control rat. **C** and **D** Autoradiographs of sections from a rat treated with TMT 4h earlier. **E** and **F** Autoradiographs of sections from a rat treated with TMT 2 weeks earlier. **G** and **H** Autoradiographs of sections from a rat treated with TMT 12 weeks earlier. Note the apparent loss of NMDA receptors in the stratum oriens and stratum radiatum of the CA3 region at 2 and 12 weeks after TMT treatment (open arrows). *dg* dentate gyrus; *ca3* CA3 field of Ammon's horn; *ca2* CA2 field of Ammon's horn; *ca1* CA1 field of Ammon's horn; *cx* cortex; *str* caudal striatum; *th* thalamic nuclei; *pir cx* piriform cortex, *amyg* amygdaloid nuclei

highest ^{3}H-TCP binding was seen in the CA1 field of Ammon's horn (334 ± 12 fmol/mg tissue). In particular, the stratum oriens and the stratum radiatum of the CA1 field were densely labeled, while the stratum lacunosum-moleculare was less labeled and the pyramidal layer unlabeled. High binding was also seen in the CA3c (233 ± 14 fmol/mg tissue) and CA3ab (199 ± 21 fmol/mg tissue) fields of Ammon's horn. In the CA3 field, stratum oriens and stratum radiatum were densely labeled, while no or little labeling was seen in the stratum lucidum and the pyramidal layer. A high level of binding was also seen in the dentate gyrus (289 ± 14 fmol/mg tissue); in particular the outer parts of the molecular layer were densely labeled, whereas no specific labeling was seen in the inner layers of dentate gyrus. In addition, high ^{3}H-TCP binding was found in layer 1 to 4 in neocortex (245 ± 12 fmol/mg tissue) and in piriform cortex (215 ± 9 fmol/mg tissue) as well as in striatum (173 ± 13 fmol/mg tissue).

No significant effects were seen in the ^{3}H-TCP binding 4h after TMT administration in any of the brain areas studied (Figs. 2 and 3). However, at 2 and 12 weeks following TMT an apparent loss of binding was seen in stratum oriens and stratum radiatum of the CA3c field of Ammon's horn. Also, a tendency towards reduced ^{3}H-TCP binding was observed in the CA3ab field, in caudal striatum and in piriform cortex at 2 weeks. At 12 weeks following TMT exposure, a significant reduction was also found in caudal striatum and in piriform cortex (Fig. 3).

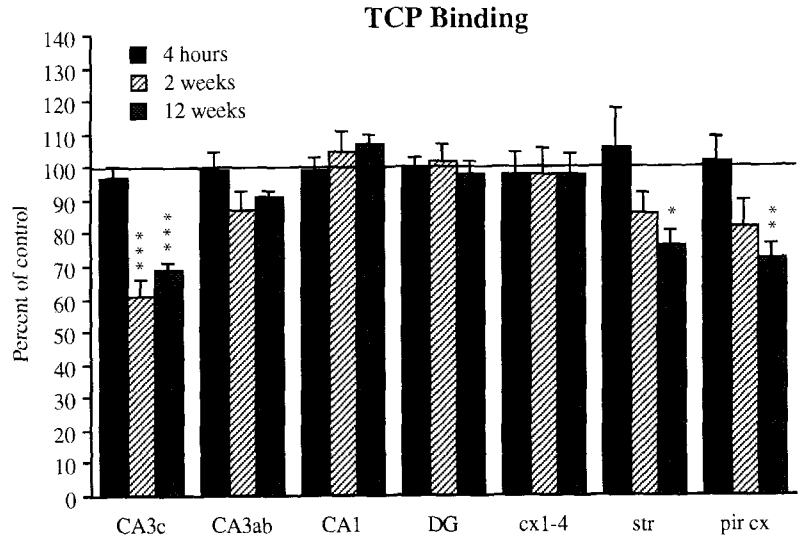


Fig. 3. Regional *in vitro* binding of 3H-TCP to NMDA receptors in frontal sections of the dorsal hippocampus of the rat brain as studied using autoradiography 4h, 2 weeks and 12 weeks after TMT administration. The specific binding was determined by subtracting labeling obtained in sections incubated with ^{3}H-TCP in the presence of 20 μM PCP. Values are expressed as mean percent binding ± SEM of the mean binding in control animals (n = 5-6). Statistical comparison was performed using Student's t-test; * = $p < 0.05$, ** = $p < 0.01$ and *** = $p < 0.001$. *CA3c* = CA3c field of Ammon's horn; *CA3ab* CA3ab field of Ammon's horn; *CA1* CA1 field of Ammon's horn; *DG* dentate gyrus, inferior (medial) blade; *cx 1-4* neocortex layer 1 to 4; *str* caudal striatum; *pir cx* piriform cortex

^{3}H-KA receptor autoradiography

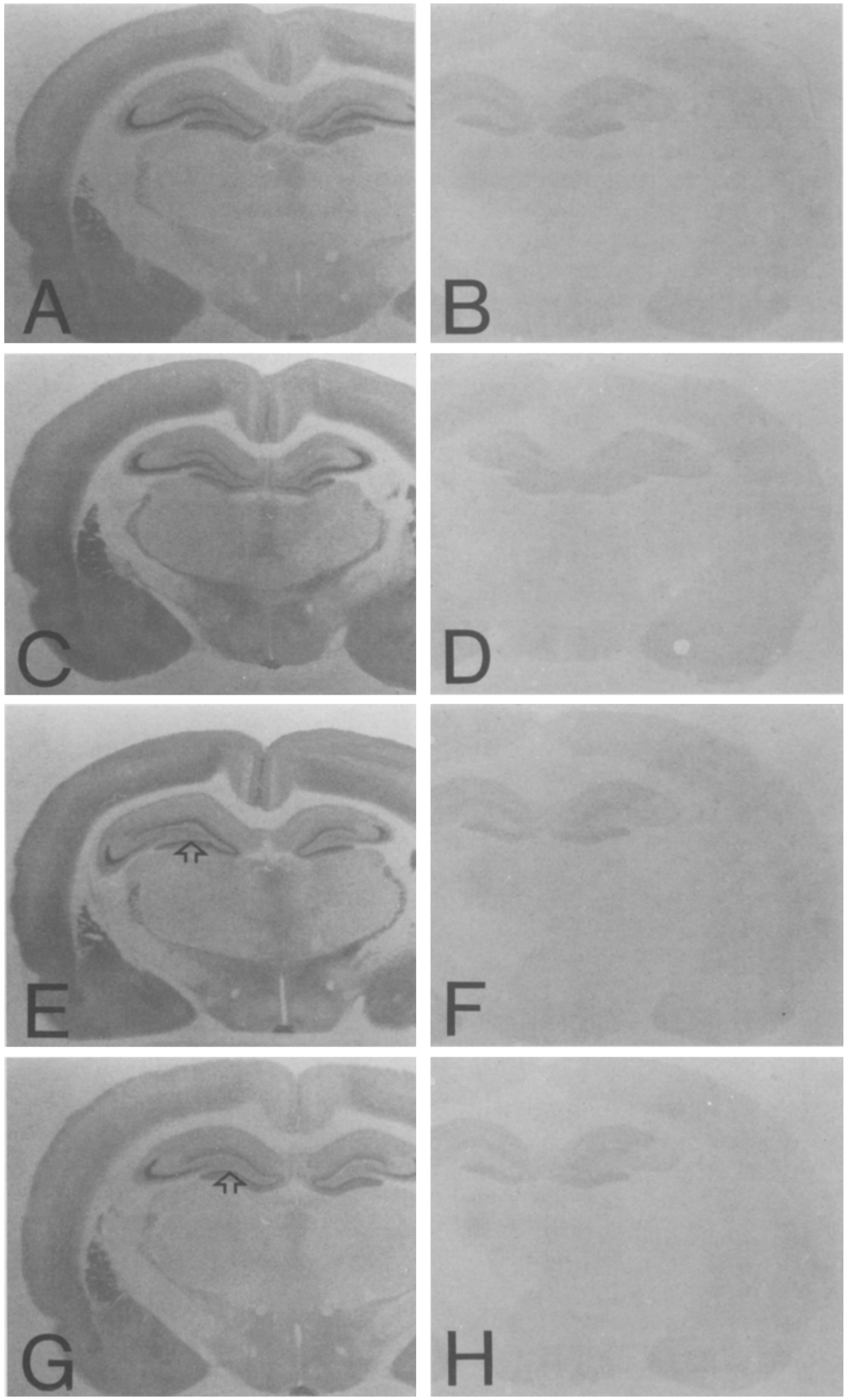
The ^{3}H-KA binding showed a regionally restricted labeling in the autoradiographs, which could be displaced to a major extent (80–90%) with KA (Fig. 4). The highest 3H-KA binding was seen in stratum lucidum and pyramidal layer of the CA3ab field of Ammon's horn (161 ± 15 fmol/mg tissue). Slightly less binding was seen in stratum lucidum and pyramidal layer of the CA3c field of Ammon's horn (135 ± 12 fmol/mg tissue). No KA displaceable ^{3}H-KA labeling was seen in any of the layers of the CA1 and CA2 fields of Ammon's horn. In the dentate gyrus, the inner third of the molecular layer was labeled with ^{3}H-KA (92 ± 15 fmol/mg tissue), while no other sub-fields of the dentate gyrus were labeled. High ^{3}H-KA binding was found in layers 5 and 6 in the neocortex (112 ± 9 fmol/mg tissue), while less binding was seen in the amygdaloid nuclei (68 ± 6 fmol/mg tissue) and in piriform cortex (66 ± 10 fmol/mg tissue) as well as in striatum (103 ± 14 fmol/mg tissue).

The ^{3}H-KA binding was not significantly affected 4h after TMT administration in any of the brain areas studied (Figs. 4 and 5). An extensive loss of binding was seen in stratum lucidum and the pyramidal layer of the CA3c field of Ammon's horn at 2 weeks following TMT. A minor reduction of ^{3}H-KA binding was also seen in the CA3ab field 2 weeks after TMT. The loss of ^{3}H-KA binding in the CA3c field persisted until 12 weeks after TMT exposure. At 12 weeks following TMT, no effect was seen in the CA3ab field. Furthermore, the TMT treatment did not affect the ^{3}H-KA binding in any other region studied (Fig. 5.).

Discussion

The present study demonstrates that acute TMT administration in adult rats leads to long-lasting decreases in ^{3}H-TCP and ^{3}H-KA binding in restricted regions of the limbic system. It has been shown that ^{3}H-TCP, a derivative of the dissociative anesthetic PCP, can be used to label a channel site within the NMDA sensitive excitatory amino acid receptor complex (Maragos et al., 1986) and that ^{3}H-KA is an appropriate ligand for the kainate excitatory amino acid receptor (Patel et al., 1986). The anatomical distribution of the ^{3}H-TCP and the ^{3}H-KA binding was similar as previously described for NMDA and kainate receptors (Cotman et al., 1987). Thus, in all probability the effects seen in ^{3}H-TCP and ^{3}H-KA binding reflect a TMT-induced reduction in NMDA and kainate receptors.

The loss of NMDA and kainate receptor binding occurred in regions previously described to manifest neuronal loss after TMT treatment in adult rats, i.e. the hippocampal CA3 region, piriform cortex as well as striatum (Brock and O'Callaghan, 1986; Chang and Dyer, 1983; Bouldin et al., 1981; Brown et al., 1979; Woodruff and Baisden, 1990). Indeed, our histological evaluation indicated an overlap in the neuronal lesions and the loss of NMDA and kainate receptor binding. In the CA3 region, a similar loss of NMDA and kainate receptor binding was detected after TMT exposure. However, in striatum and piriform cortex NMDA receptor binding was significantly reduced at 12 weeks following TMT, whereas kainate receptor binding was unaffected. These differ-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ences may reflect effects of TMT on selective neuronal populations enriched with NMDA receptors in piriform cortex and striatum, whereas TMT sensitive pyramidal neurons in hippocampus may hold both NMDA and kainate receptors on distal and proximal dendrites, respectively. The loss of TCP binding in pirifom cortex indicates that TMT induces a neuronal lesion in that region. It has previously been shown that extensive lesions of the piriform/entorhinal cortex, which provides the dentate gyrus with perforant path afferents, lead to a reactive synaptogenesis (axonal sprouting) of cholinergic septal afferents to dentate gyrus (Nadler et al., 1977). Furthermore, an expansion of the kainate receptor field in the molecular layer of the dentate gyrus is seen after such lesions (Ulas et al., 1990). A similar sprouting of acetylcholinesterase stained fibers has been shown to occur in TMT-treated rats (Woodruff and Baisden, 1990). However, no changes in kainate receptors or NMDA receptors were found in the dentate gyrus in the present study. This may be due to that an extensive lesion of perforant path neurons did not occur following the TMT administration. Interestingly, marked effects were seen on NMDA and kainate receptor binding in the CA3 region without any obvious changes were seen in the dentate gyrus, an important input region of the dentate gyrus.

The mechanisms involved in TMT neurotoxicity are largely unknown. Trialkyltins are not known to combine with many macromolecules, while they do interfere with mitochondrial function, adenosine triphosphate (ATP) synthesis and Na^+/K^+ ATPase of cell membranes (Aldridge et al., 1977; Selwyn 1976). Furthermore, TMT has been shown to induce glutamate release both *in vitro* and *in vivo* (Brodie et al., 1990; Patel et al., 1990). Thus, TMT administration seems to lead to a loss of energy dependent membrane functions such as transmitter release and uptake. TMT-induced increase in extracellular glutamate levels may induce enhanced activation of excitatory amino acid receptors, which may initiate 'excitotoxic' processes as has been suggested in a number of neurodegenerative conditions (see Choi, 1988; Geenamyre, 1986). Actually, it has been suggested that the neuropathology of TMT is dependent on a 'hyperexcitability' cascade of events in the limbic system (Chang, 1986). According to this hypothesis, important excitatory input regions to the hippocampal formation, e.g. piriform/entorhinal cortex, become activated by TMT, which in turn excite dentate gyrus neurons via the perforant path, followed by activation of CA3 pyramidal neurons. Regionally selective lesions occurring after TMT exposure would then be due to differences in stimulation along this network (Chang, 1986). The present results provide some support for the 'hyperexcitability' cascade hypothesis, since a selective loss of NMDA and kainate receptors was seen in

Fig. 4. Autoradiographs of *in vitro* binding of ^{3}H-KA to kainate receptors in frontal sections of the dorsal hippocampus of the rat brain (**A, C, E** and **G**) and autoradiographs of sections incubated with ^{3}H-KA in the presence of 100 μM KA to define non-specific binding (**B, D, F** and **H**). **A** and **B** Autoradiographs of sections from a control rat. **C** and **D** Autoradiographs of sections from a rat treated with TMT 4h earlier. **E** and **F** Autoradiographs of sections from a rat treated with TMT 2 weeks earlier. **G** and **H** Autoradiographs of sections from a rat treated with TMT 12 weeks earlier. Note the apparent loss of KA receptors in the pyramidal layer of the CA3 region at 2 and 12 weeks after TMT treatment (open arrows)

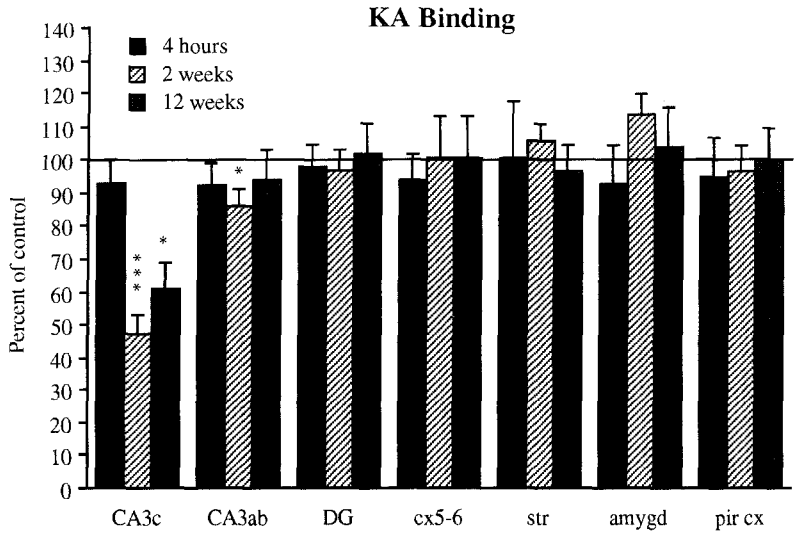

Fig. 5. Regional *in vitro* binding of ^{3}H-KA to kainate receptors in frontal sections of the dorsal hippocampus of the rat brain as studied using autoradiography 4h, 2 weeks and 12 weeks after TMT administration. The specific binding was determined by subtracting labeling obtained in sections incubated with ^{3}H-KA in the presence of 100 μM KA. Values are expressed as mean percent binding $\pm$ SEM of the mean binding in control animals (n = 4-6). Statistical comparison was performed using Student's t-test; * = $p < 0.05$, ** = $p < 0.01$ and *** = $p < 0.001$. *CA3c* CA3c field of Ammon's horn; *CA3ab* CA3ab field of Ammon's horn; *DG* dentate gyrus, inferior (medial) blade; *cx5-6* neocortex layer 5 to 6; *str* caudal striatum; *amygd* amygdaloid nuclei; *pir cx* piriform cortex

defined regions of the limbic system with high receptor densities. It has been shown that systemic PCP administration in a period before and after TMT administration counteracts certain TMT-induced changes in locomotion and spatial learning (Early et al., 1990), suggesting that NMDA channel blockers do interfere with TMT toxicity. On the other hand, no significant effects were seen on TCP or KA binding 4h following TMT, whereas at this time-point alterations in growth factor expression are seen (Lindström et al., 1992). This indicates that TMT does not directly interact at the recognition sites for TCP or KA at early time points. Thus, it is presently unclear whether TMT interacts directly or indirectly with excitatory amino acid receptor-mediated functions.

The limbic system, and in particular the hippocampal formation, has been shown to be critically involved in a number of cognitive functions (see Walker and Olton, 1984). Moreover, excitatory amino acid neurotransmission appears to play a crucial role in such functions (e.g. Danysz el al., 1988; Lee et al., 1993). Hence, it is likely that TMT-induced lesions of excitatory neuronal pathways in the limbic system, as has been demonstrated in the present study, are involved in the cognitive disabilities detected in the period following TMT exposure (see Introduction). However, TMT intoxication also leads to long-term alterations in other neuronal systems supposed to be important for cognitive abilities. Following an early reduction in monoamine levels, enhanced levels of serotonin and noradrenaline are seen suggesting a sprouting of monoamine fibers in the hippocampal formation after TMT (Andersson et al., 1994). Also, a sprouting of

cholinergic fibers occur after TMT exposure (Woodruff and Baisden, 1990), concomitant with a reduction in muscarinic receptors (Early et al., 1989) and corticosteriod binding (Messing et at., 1988). It is therefore apparent that a complex pattern of alterations take place in various transmitter systems following TMT exposure; changes that could be implicated in both pathological as well as compensatory effects on behavioral functions. Of particular interest to note in the present study is the altered NMDA receptor binding in striatum, since motor disturbances, such as hyperactivity, are consistent findings after TMT lesions. The hyperactivity observed after TMT administration in previous reports (e.g. Ruppert et al., 1982) may also be a result of decreased output of hippocampus to extrapyramidal regions. Damage in hippocampus presumably disrupts the output from this region to nucleus accumbens (Totterdell and Smith, 1989), which could affect locomotor activity (Morris, 1983; Whishaw and Mittelman, 1991). However, alterations in motor functions after TMT exposure may also reflect direct effects on excitatory amino acid neurotransmission in extrapyramidal regions.

In summary, TMT exposure in adult rats leads to extensive and regionally selective reductions of NMDA and kainate excitatory amino acid receptors in the limbic system. These alterations appear to primarily reflect a loss of pyramidal cells in hippocampus, which are highly dependent on excitatory amino acid neurotransmission, and are particularly vulnerable to TMT toxicity. Lesions in this neuronal network may further be involved in the behavioral effects, e.g. cognitive disabilities, described to occur in the period following acute TMT exposure.

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