DIFFERENTIAL EFFECT OF TCDD ON BRAIN SEROTONIN (5HT) METABOLISM IN A TCDD-SUSCEPTIBLE AND A TCDD-RESISTANT RAT STRAIN.

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The mechanism of acute toxicity of the environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has not yet been resolved. The over 300-fold difference in the LD_{50}-values for TCDD between two rat strains, Long-Evans (L-E; LD_{50} ca. 10 μg/kg) and Han/Wistar (H/W; LD_{50} >3000 μg/kg) has provided a new powerful tool for studies of TCDD toxicity. A striking disparity between the rat strains emerges in their feeding behaviour after TCDD: although both strains initially decrease feed intake, only H/W rats resume eating in about a week[1]. As central monoamines have been implicated in the regulation of feed intake, it was of interest to compare the effects of TCDD on brain neurochemistry between the two rat strains as a function of time.

Adult male rats (11-12 wk) of both strains were injected ip with a single dose of TCDD (50 μg/kg; LD_{100} for L-E, nonlethal to H/W) or vehicle. They were then monitored for daily food intake and body weight. Four or 10 days after TCDD exposure half the rats were injected with α-methyl-p-tyrosine (AMPT) or vehicle. AMPT is a competitive CA synthesis inhibitor. It rapidly and linearly declines CA concentrations in the brain, the degree of which reflects ongoing catecholaminergic neuronal activity. Three hr after AMPT or vehicle injections, rats were decapitated and brains were rapidly removed and dissected into nine regions: hypothalamus, median eminence, olfactory bulb, hippocampus, midbrain+-thalamus, medulla, striatum, cerebellum and cortex. They were then frozen in liquid nitrogen. Regional catecholamines (noradrenaline and dopamine) and indoleamines (5HT, 5-hydroxyindoleacetic acid [5HIAA], tryptophan; from rats not injected with AMPT) were then determined by HPLC with electrochemical detection. Catecholaminergic neuronal activity was estimated by relating the CA concentrations in AMPT-treated rats to those in saline controls.

As expected, L-E rats decreased dramatically their daily food intake and body weight after TCDD exposure while H/W rats responded only marginally to TCDD administration (fig. 1). Four days after exposure, L-E rats exhibited 36 and 43% (mean increases from all brain areas) elevated levels of the 5HT metabolite 5HIAA and its precursor tryptophan, respectively, in all brain regions suggesting increased serotonergic activity by TCDD (fig 2). There was also a tendency toward increased 5HT levels in most brain areas with statistical significance being reached in olfactory bulbs and midbrain+thalamus. The elevations of 5HIAA and tryptophan were still present 10 days after exposure. In contrast, the resistant H/W rats exhibited only marginally elevated tryptophan and 5HIAA four days after TCDD, and these changes had levelled off by 10 days after TCDD administration (fig 2.). When another set of L-E rats were pair-fed for 4 days to their TCDD-treated counterparts, there was a slight tendency toward increased 5HIAA and tryptophan levels across all brain areas measured (fig 3). However, this change was clearly less pronounced than that in TCDD-treated L-E rats. Statistical significance was reached in midbrain only. TCDD affected surprisingly little noradrenaline or dopamine metabolism. The decay of noradrenaline and dopamine after inhibition of their synthesis by AMPT was not markedly affected in any brain region by TCDD (fig 4). Some scattered changes in catecholamines were observed, but both strains responded by and large similarly. Thus it is likely that TCDD does not markedly affect brain catecholaminergic systems.

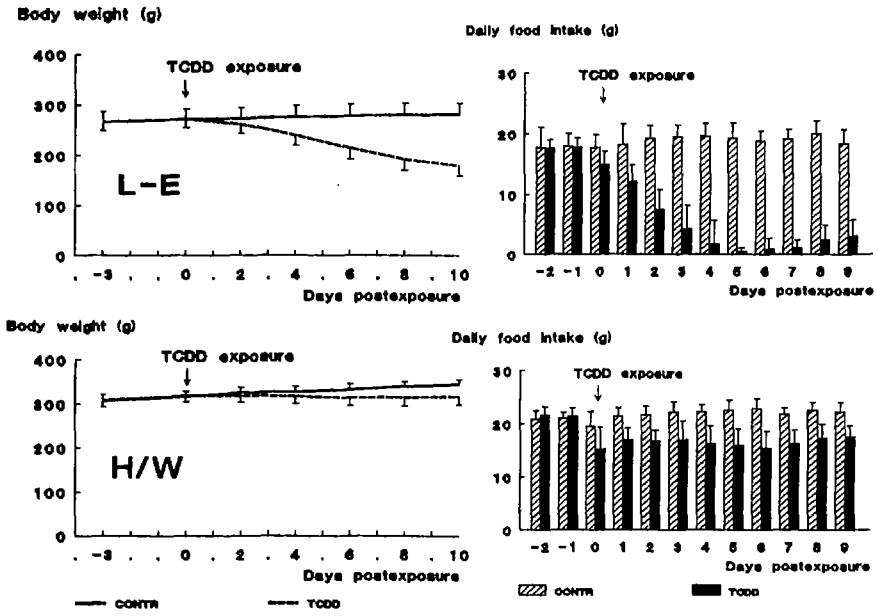

Figure 1. Body weights and 24h food intake of L-E (top) and H/W (bottom) rats in the 10-day experiment. N=12 /group.

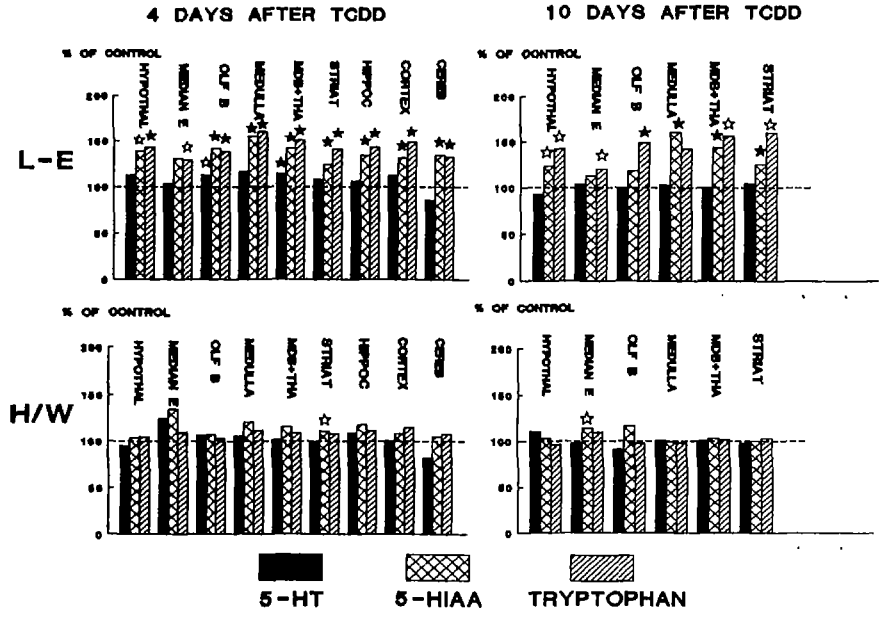

Figure 2. Effect of TCDD on the levels of 5HT, 5HIAA and tryptophan in discrete brain areas. The bars represent mean concentrations relative to control values. N=6. Open asterisk $p<0.05$, closed $p<0.01$; t-test.

The increases in the serotonin precursor tryptophan and its metabolite 5HIAA in the sensitive L-E rats alone by TCDD imply that increased serotonergic activity may be, indirectly or directly, associated with TCDD lethality. As previously reported[2], TCDD increases plasma tryptophan concentration in Sprague-Dawley rats. Therefore, the induced activity of serotonergic systems may be secondary to enhanced entry of tryptophan from plasma to brain in TCDD-treated L-E rats and warrants further studies.

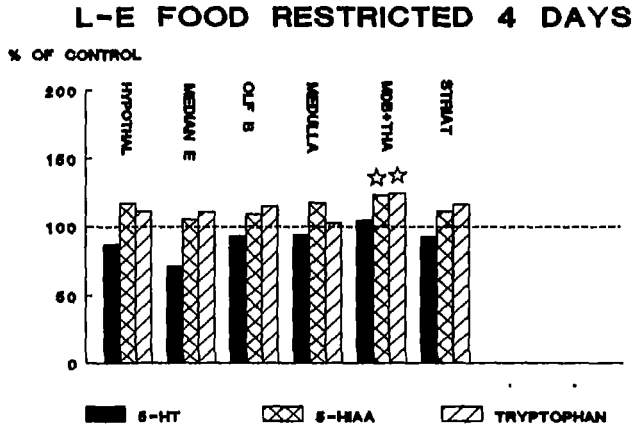

Figure 3. Effect of pair-feeding on the levels of 5HT, 5HIAA and tryptophan in discrete brain regions. Pair-fed rats received the same amount of food that TCDD-treated L-E rats consumed daily during the 4-day experiment.

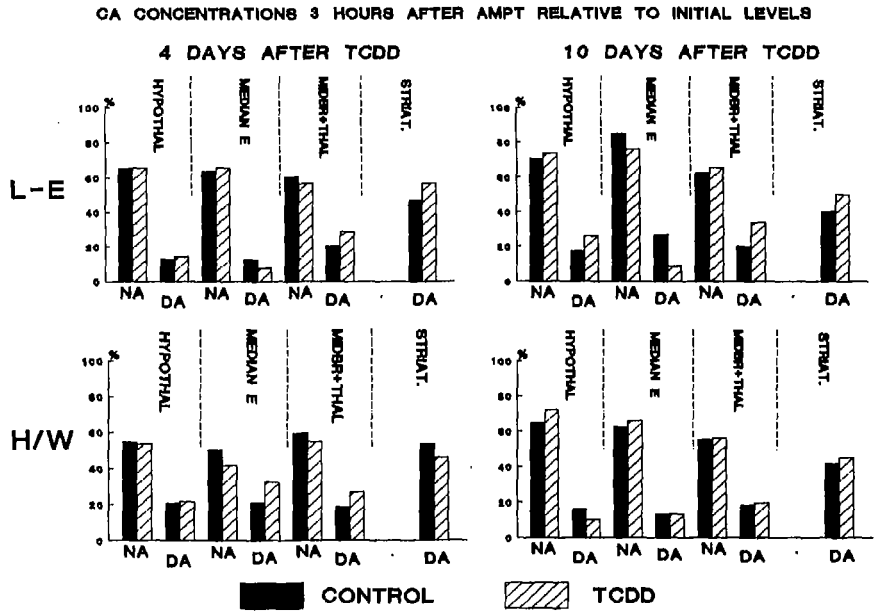

Figure 4. Effect of TCDD on the decay of CA:s in brain areas after inhibition of their biosynthesis by AMPT. The data are shown as per cent of the corresponding concentrations in saline treated rats. N=6 /group. The smaller the bar, the higher the turnover rate.

We are grateful to Ms. Minna Holopainen and Ms. Arja Tamminen for their technical assistance. This work was financially supported by the Academy of Finland.

References:
1. Tuomisto J, Pohjanvirta R, Sci Tot Environ 1991;106:21-31.
2. Rozman K, Pfeifer B, Kerecsen L, Alper RH. Arch Toxicol 1991;65:124-128.