The Reduction of Plasma Melatonin Concentration by TCDD Is Not Due to Enhanced Metabolism of the Hormone

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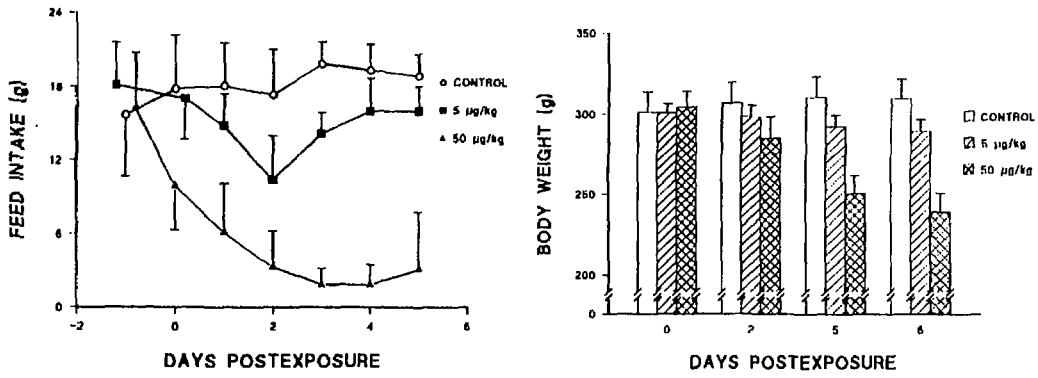
The hormone secreted by the pineal gland, melatonin, is the most important signal of the prevailing ambient lighting conditions in the body. Our laboratory has demonstrated that exposure to TCDD results in a drastic (about 50%) reduction of plasma melatonin concentration in rats. This effect appears to be independent of strain (and hence of susceptibility to the acute lethality of TCDD) and time of day. It further seems to develop fairly rapidly (within 30 hr) and persist a long time (at least 28 days)[1,2].

Our recent study failed to find any morphological lesion at either the light or electron microscopical level in the pineal glands of TCDD-treated rats[2]. That outcome would be compatible with induced peripheral metabolism of melatonin by TCDD. The half-life of plasma melatonin is only 10 to 40 min principally due to effective biotransformation by hepatic microsomal enzymes[3]. In the liver, melatonin is metabolized to 6-hydroxymelatonin which is rapidly conjugated mainly with sulphate ions[4]. Over 95% of the excretion of melatonin occurs as 6-hydroxymelatonin sulphate (6-OHMS) in the urine[4]. The daily excretion of hydroxylated melatonin in the urine reflects reliably melatonin secretion by the pineal gland[5]. TCDD is a well-established inducer of both Phase I (CYPIA1 and CYPIA2) and Phase II (e.g. UDPGT) drug-metabolizing enzymes in the liver. Therefore, in the present study we examined the effect of TCDD exposure on the excretion of both melatonin and 6-OHMS in rat urine.

The most TCDD-susceptible substrain of rats, Long-Evans (Turku AB), was used. A total of 30 male rats were transferred at the age of 4-5 weeks into an animal room with a reversed lighting rhythm (lights on from 09.00 hr to 17.00 hr), and allowed to acclimatize to the conditions for 6 weeks. TCDD was dissolved in corn oil (10 μg/ml) and administered as a single ip injection at 0, 5 or 50 μg/kg (10 rats/group) between 08.00 hr and 09.00 hr on day 0. The lower dose of TCDD is usually nonlethal and the higher lethal to all rats of this substrain. The rats were housed in plastic metabolic cages (Tecniplast®), and their daily feed intake was recorded and 24-hr urine production collected. The urine melatonin concentration was determined by a sensitive RIA method[6,7]. 6-OHMS was also analyzed by a specific RIA[8] in urine samples collected on days 3 and 5 after exposure.

TCDD exposure caused a striking and dose-dependent decline in both feed intake and body weight (Figs. 1a & 1b). The excretion of melatonin in urine exhibited a similar dose-related decrease starting from day 1 after exposure (at the dose of 50 μg/kg) and continuing to the end of the observation period (Fig. 2). Likewise, the excretion of 6-OHMS was reduced by TCDD at both time points of measurement (Fig. 3).



Figs. 1a & 1b. *The effect of TCDD on daily feed intake and body weight gain in male Long–Evans (Turku AB) rats. Mean ± SD, n=10/group.*

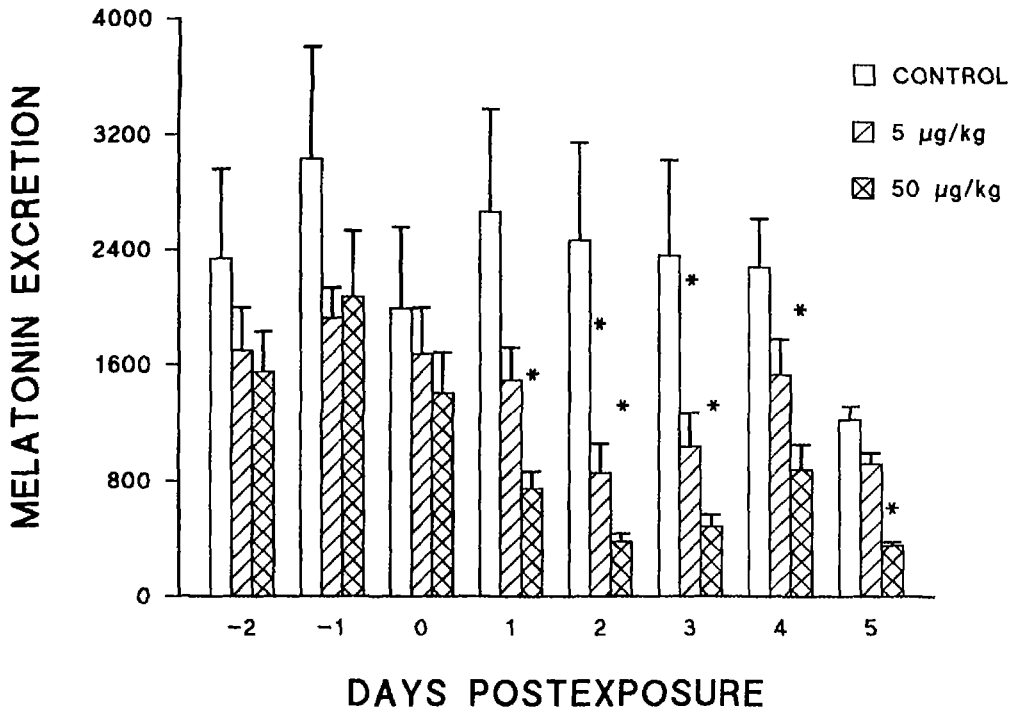


Fig. 2. *Excretion of melatonin in urine (pg/24 hr) in TCDD–treated and control rats. Mean ± SEM; n=10. The asterisks denote statistically significant (p<0.05) differences vs. control.*

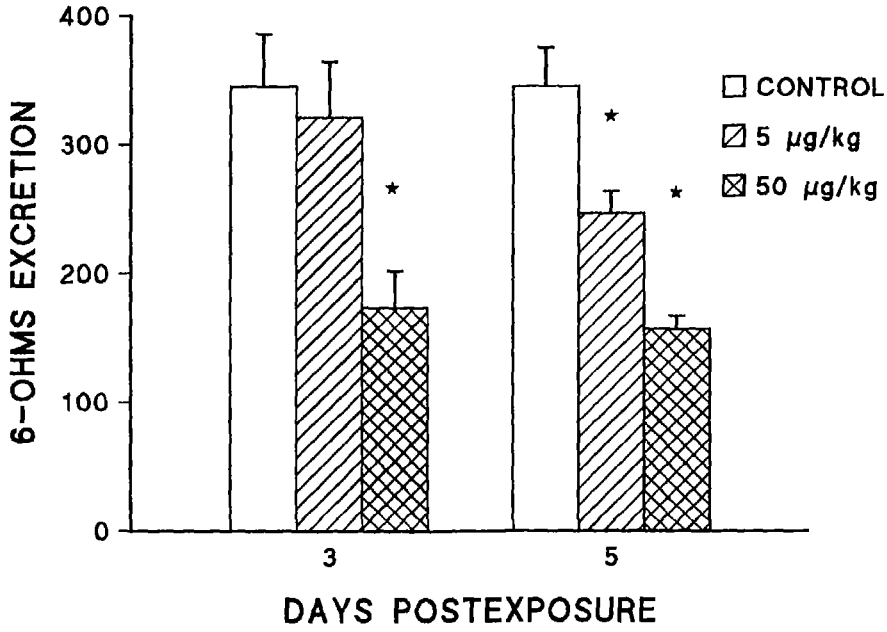


Fig. 3. *Excretion of 6-OHMS in urine (ng/24 hr) in TCDD-treated and control rats. Mean ± SEM; n=10. The asterisks denote statistically significant (p<0.05) differences vs. control.*

The present results do not support the assumption of induced peripheral metabolism of melatonin by TCDD as the reason for the reduced plasma and urine melatonin levels in TCDD-treated rats. In contrast, they strongly suggest impaired secretion of melatonin by the pineal gland.

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