SHORT COMMUNICATIONS

PRODUCTION OF TOLERANCE TO FENITROTHION IN MALE RATS

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Accepted January 24, 1983

It has been reported that animals can become tolerant to organophosphorus insecticides such as octamethyl pyrophosphoramid (1, 2), Systox (2) and Di-Syston (3). Misu et al. (4) have observed that the inhibition of cholinesterase activity in various organs of rats given fenitrothion in the diet was alleviated in proportion to the period of fenitrothion ingestion. They indicated that this phenomena was one of the indices of tolerance-formation toward fenitrothion; the mechanism of tolerance could be the refractoriness of cholinergic receptors to acetylcholine. Nevertheless, the mechanisms by which the tolerance develops is unknown.

The present paper investigates growth tolerance in rats that were administered daily sublethal doses of fenitrothion.

Fenitrothion (0,0-dimethyl-O-(p-nitrom-cresol) phosphorothionate, Sumitomo Chemical Co., Ltd.) was purified by alumina column chromatography (Woelm, acid form, activity I), with dry benzene as the eluting solvent, and by preparative thin-layer chromatography (developing solvent, hexane: chloroform: methanol, 7:2:1, v/v). Male Wistar rats (150-350 g body weight) were fed ad libitum with diet and water; they were maintained at 22-24°C and on a circadian cycle of 12 hr light and 12 hr dark. The rats were orally administered fenitrothion dissolved in olive oil. Control rats were given the vehicle only.

Figure 1 shows the effects of various sublethal daily oral doses of fenitrothion for 28 days on the body weight of rats. At the lowest dosage level (7.25 mg/kg/day, one-fortieth of acute LD50 value), the animals

![Graph showing body weight changes over time for different dosage levels of fenitrothion.](image)

Fig. 1. Effects on body weight of various daily oral doses of fenitrothion given for 4 weeks. Values are expressed as the mean body weight. Four or five rats were used in each group. Administration of fenitrothion: , olive oil; --- , 7.25 mg/kg/day; ------ , 14.5 mg/kg/day; --- , 29.0 mg/kg/day. In the highest group, the administration was stopped at 2 weeks.
exhibited no cholinergic signs from fenitrothion during the 4 week administration period. The growth rate of animals was depressed in each of the three groups in a dose dependent manner. Maximum depression of growth rates was observed at 10 and 6 days after administration of fenitrothion at 14.5 and 29.0 mg/kg/day, respectively. A tremor of the whole body and ataxia were observed on the 6th to 10th day and on the 3rd to 6th day of the administration in the 14.5 mg/kg/day and 29.0 mg/kg/day groups, respectively. In particular, there were also observed lacrimation, salivation and urination in the highest dose group (29.0 mg/kg/day) in parallel with the reduction of growth. However, recovery of the growth rates and disappearance of the cholinergic symptoms were observed gradually after maximum inhibition of growth rate in spite of continued daily treatment with fenitrothion. The decrease of cholinesterase activity in the liver and plasma was measured at the 2nd, 4th, 6th, 14th and 28th days of administration and was dependent on the dose levels of fenitrothion. The decrease in cholinesterase activity in the liver and plasma showed a tendency to recover after the 4th to 6th day of the administration in each group (data not shown). This result indicates that rats can become tolerant to repeated daily administration at dose levels of 14.5 and 29.0 mg/kg/day.

Also we investigated the effects of pretreatment of fenitrothion on growth rates and lethality of the administration of fenitrothion (58.0 mg/kg/day, one-fifth of acute LD50 value) for 10 days. Figure 2 shows the effects of pretreatment of male rats for 5 days with various oral doses of fenitrothion on the body weight of rats given 58.0 mg/kg/day fenitrothion for 10 days after the pretreatment period. At the commencement of the second dosage schedule, the body weight of rats pretreated with fenitrothion was depressed according to the dose (29.0, 14.5 and 7.25

Fig. 2. Effects of pretreatment with various daily oral doses of fenitrothion given for 5 days on the body weight of rats post-administered with fenitrothion (58.0 mg/kg/day) for 10 days. Values are expressed as body weight (left, mean±S.E.) and as percent of the body weights (right) at the first day of post-administration in each group. Five rats were used in each group. Each * represents the death of one rat. Pretreatment of fenitrothion: —●—, olive oil; —○—, 7.25 mg/kg/day; —▲—, 14.5 mg/kg/day; —■—, 29.0 mg/kg/day. § Statistical significance: P<0.001, control vs. 14.5 mg/kg/day; P<0.001, control vs. 29.0 mg/kg/day; P<0.01, 14.5 mg/kg/day vs. 29.0 mg/kg/day.
mg/kg/day) of pretreatment (Fig. 2, left). However, in spite of continued daily treatment with fenitrothion, the growth rate began to recover, and the severe cholinergic signs (lacrimation, ataxia, salivation, urination and tremor) disappeared at 2 to 3 days following the repeated administration of fenitrothion in the high dose pretreatment groups (14.5 and 29.0 mg/kg/day, Fig. 2, right). Moreover, one-fifth of the rats were dead at 2 and 3 days after post-administration in the high pretreatment groups of 29.0 and 14.5 mg/kg/day, respectively. On the contrary, high mortality (80% and 100%) and retardation of growth rates were observed in the low dose pretreatment (7.25 mg/kg/day) and non-pretreated groups, respectively.

Thus, it seems likely that repeated sublethal administration of fenitrothion might produce tolerance in male rats. This present results indicates that it is possible to acquire tolerance to fenitrothion by repeated treatment with sublethal doses. Now detailed work is under way to clarify the mechanism of tolerance-formation.

References