Developmental Neurotoxicity of Endocrine Active Compounds

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Altering the hormonal milieu can affect the developing (and adult) brain. Endocrine modulators have sparked much controversy regarding the extent to which general exposure of the population occurs and whether they contribute to the incidence of developmental anomalies, including behavioral deficits, in exposed populations. Experimental evidence exists to support the hypothesis that prenatal or postnatal exposure to an antiandrogenic chemical can affect brain development. For example, it is well established that the development of a variety of brain structures (i.e., sexually dimorphic nuclei (SDN)) is under hormonal control, and SDN and reproductive tract development occur simultaneously. The initial focus of this project was to characterize the potential of the organophosphate insecticide (OP) fenitrothion to induce adverse health effects in animals that are associated with an antiandrogenic mode of action. This project examined whether prenatal or postnatal exposure to fenitrothion is associated with altered brain development or function in rodents. Pregnant rats (n = 5-6 litters/group) were orally dosed with corn oil (vehicle) or fenitrothion (20 or 25 mg/kg/day) from gestation day (GD) 12 through 21. Flutamide (100 mg/kg, s.c.), a potent nonsteroidal androgen receptor antagonist, was used as a positive control. Flutamide in methylcellulose (n=5 litters) or methylcellulose alone (n=4 litters) was given on postnatal days (PND) 1, 5, 15, and 20. Offspring were euthanized after reaching sexual maturity (females 60-65 days old, and males 96-105 days old). Brains from 2 males and 2 females per litter were evaluated for sexually dimorphic nucleus of the medial preoptic area (SDN-POA) volumes. Transient reproductive effects, including reduced anogenital distance in PND1 males and increased retention of areolae in PND13 male offspring were observed following fenitrothion exposure. These effects did not persist into adulthood. Tremors, increased lacrimation, decreased body weight gain, and a decrease in the number of live pups were observed in the fenitrothion-exposed dams. SDN-POA volume was decreased in the male rats exposed postnatally to flutamide, but similar changes were not observed following prenatal fenitrothion exposure. Instead, there was a dose-related increase in the SDN-POA volume in males and a dose-related decrease in SDN-POA volume in females exposed to fenitrothion. Based on the transient nature of the reproductive alterations seen, and the atypical change in the SDN-POA volumes, inhibition of cholinesterase activity remains the critical endpoint for the risk assessment of fenitrothion.

Another objective of this project was to characterize the association between in utero exposure to the organophosphate insecticide fenitrothion and tissue esterase activity and fenitrothion concentrations in the rat dam and fetus. Time-mated, 8-week-old rats were gavaged on gestation day 19 with 0, 5, or 25 mg fenitrothion/kg. Fenitrothion was absorbed rapidly from the gastrointestinal tract, with peak maternal and fetal blood levels observed 0.5-1 hr after dosing. Fenitrothion concentrations in maternal and fetal blood were virtually identical and demonstrated a dose-response relationship. Acetylcholinesterase and carboxylesterase activities in maternal liver and blood and in fetal liver and brain decreased within 30-60 min of fenitrothion exposure. Esterase inhibition occurred at a fenitrothion dose (5 mg/kg) that has not been previously associated with reproductive toxicity, suggesting that esterase inhibition should be considered as the critical effect in risk assessments for this pesticide.

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