FUNDAMENTAL AND APPLIED TOXICOLOGY 17, 543–549 (1991)

Characterization of *o,p'*-DDT-Stimulated Contraction Frequency in Rat Uterus *in Vitro*[1]

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Characterization of *o,p'*-DDT-Stimulated Contraction Frequency in Rat Uterus *in Vitro*. JUBERG, D. R., WEBB, R. C., AND LOCH-CARUSO, R. (1991). *Fundam. Appl. Toxicol.* **17**, 543–549. Exposure to organochlorine pesticides, including DDT, has previously been associated with premature birth. Using an improved protocol to characterize dose and time dependent responses, the present report extends a preliminary finding by this laboratory that *o,p'*-DDT directly stimulates uterine contractility. Contraction frequency was determined in longitudinal uterine strips from pregnant rats under isometric force conditions. Following equilibration, the uterine strips were monitored for a 1-hr baseline period, then treated with *o,p'*-DDT or ethanol (solvent control) for 3 hr, followed by 3 hr without test substance. During exposure to 100 μM *o,p'*-DDT, the frequency of contraction significantly increased by 66% relative to matched controls. After removal of *o,p'*-DDT from the medium, the frequency of contraction continued to increase in uterine strips exposed to 50 and 100 μM *o,p'*-DDT. A dose effect was clearly observed during the post-treatment period, with 50 and 100 μM *o,p'*-DDT significantly increasing contraction frequency by 39 and 104% relative to controls. No significant differences in contraction frequency were observed with 10 μM *o,p'*-DDT during any test period. These data show that *o,p'*-DDT directly stimulated isometric contractions in rat uterine strips. © 1991 Society of Toxicology.

DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane) is perhaps the best known insecticide manufactured. While its usage is now restricted in the United States and several other countries, it remains an environmental contaminant of toxicological concern. Widespread exposure of human populations to DDT is reflected by its prevalence in serum samples (Nhachi and Kasilo, 1990; Violante *et al.*, 1986; D'Ercole *et al.*, 1976), and the potential for cumulative exposure is indicated by the positive correlation of human DDT levels with age (D'Ercole *et al.*, 1976; Mussalo-Rauhamaa *et al.*, 1988; Kreiss *et al.*, 1981). In many ways, DDT is a prototype for those chlorinated compounds characterized as resistant to environmental degradation, biomagnified in the food chain, poorly metabolized, and highly retained in the body (Murphy, 1986).

Women are a population of special significance with respect to organochlorine pesticide exposure, in part due to possible adverse effects on pregnancy. Of notable concern is that exposure to DDT and other organochlorine compounds has been associated with preterm birth in several mammalian species, including California sea lions (DeLong *et al.*, 1973), rabbits (Hart *et al.*, 1971), and humans (Saxena *et al.*, 1980, 1981; Wassermann *et al.*, 1982). A mechanistic basis for this association has not been explored. Although it has been suggested that chlorinated compounds may precipitate labor by altering hormonal status (Wassermann *et al.*, 1982), experimental support of this mechanism is lacking.

Technical grade DDT consists primarily of *p,p'*-DDT and *o,p'*-DDT. The major metab-

[1] This study was presented at the 30th Annual Meeting of the Society of Toxicology in Dallas, TX, February 25 through March 1, 1991.

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0272-0590/91 $3.00

olite of DDT in humans is *p,p'*-DDE; this is often the most common form of DDT detected in human tissues, although substantial amounts of *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDD have also been found (D'Ercole *et al.*, 1976; Mussalo-Rauhamaa *et al.*, 1988). A recent report showed that *o,p'*-DDT, *p,p'*-DDT, and *p,p'*-DDD residues were detected in substantially greater amounts (1–13 ppm) in drinking water than was *p,p'*-DDE (0.05–0.09 ppm) (Dikshith *et al.*, 1990). This suggests that the *p,p'*-DDE levels observed in human tissue samples may reflect environmental exposure to DDT isomers other than *p,p'*-DDE, followed by human metabolism to *p,p'*-DDE. In our investigation, we chose the *o,p'*-DDT isomer because it has significant estrogenic effects on the uterus of numerous species, including rat, and it is a primary component of the technical grade preparation to which plants, animals, and humans are initially exposed (Galand *et al.*, 1987).

We recently reported that *in vitro* overnight exposure at 4°C to 100 μM *o,p'*-DDT stimulates subsequent contraction activity in rat uterine strips (Juberg and Loch-Caruso, 1991). In the present study, we describe an improved testing protocol for assessment of uterine contraction frequency that provides stable, phasic contractile activity prior to exposure, and has allowed us to characterize the dose- and time-related stimulatory effects of *o,p'*-DDT. The data show that the frequency of contraction increased in a dose and time dependent manner, even after removal of *o,p'*-DDT from the medium.

METHODS

Chemicals and solutions. *o,p'*-DDT (99% purity) was purchased from Crescent Chemical Co. (Hauppauge, NY). A stock solution of 20 mg/ml (56 mM) was prepared in absolute ethanol for use in all experiments.

Contractility assessment. Contraction frequency was quantified, since this was the contractility parameter found to be most affected by *in vitro* exposure to *o,p'*-DDT in an earlier study (Juberg and Loch-Caruso, 1991). For each experiment, a single longitudinal strip was excised from the fetal side of one of the uterine horns of a midgestation (Day 10) Sprague–Dawley rat, and cut in tandem from cervical to ovarian end into four smaller strips (ca. 3 mm × 10 mm). The smaller strips were assigned to an experimental group using a systematic coin toss: one of the two strips nearest to each end was assigned to a DDT group and the other strip at each end to a control group. In this manner, four strips from each animal were employed in each experimental run, two of which were exposed to *o,p'*-DDT and two of which were exposed to solvent only (control). This assignment procedure was used to reduce bias that might be introduced by disproportionate grouping of strips derived from the cervical versus ovarian end of the horn, since there may be intrinsic differences between the two regions of the uterus (Lodge and Sproat, 1981). To record isometric contractions, uterine strips were placed in 50-ml muscle baths (custom-made by the University of Michigan Glass Shop) containing physiological saline solution (PSS; 116 mM NaCl, 21.9 mM $NaHCO_3$, 11.1 mM dextrose, 4.6 mM KCl, 1.16 mM $MgSO_4(7H_2O)$, 1.16 mM $NaH_2PO_4(H_2O)$, 1.8 mM $CaCl_2(2H_2O)$, pH 7.4), two strips per bath, and allowed to equilibrate for 1 hr at 37°C (95% O_2/5% CO_2). The strips were then attached to force transducers (Grass FT-03, Quincy, MA) under 0.5 g passive tension, and the strips were depolarized with 60 mM KCl to assess maximal contractile force. The baths were rinsed free of KCl and the equilibration period was continued for 4–6 hr until regular phasic contractile activity ensued in all preparations. The strips were then monitored for 1 hr, from which baseline frequency was calculated. Following the baseline period, uterine strips were dosed with *o,p'*-DDT at final concentrations of 10, 50, or 100 μM, or with equivalent volumes of solvent only (controls) at final concentrations of 0.02, 0.09, or 0.17% (v/v) absolute ethanol. Contractions were monitored for 3 hr in the presence of test substance (treatment period), followed by 3 hr without test substance (post-treatment period). In order to maintain buffer capacity, the bathing solution was changed to fresh PSS 90 min into the treatment and post-treatment periods; replenishing PSS for the treatment period included the original concentrations of the test substance. At the conclusion of each experiment, uterine strips were again depolarized with 60 mM KCl to assess maximal contractile force and to reaffirm tissue viability. A contraction was operationally defined as a spike which initiated at baseline, exceeded 50% maximal contraction, and returned to baseline. Six or seven experimental runs were conducted with each *o,p'*-DDT concentration. This procedure differs from most reports in the literature in that uterine activity is usually assessed within 30–60 min after placement in the muscle bath. The longer equilibration period used in our study generated highly stable spontaneous baseline contractility, which typically is not observed with shorter equilibration periods.

Data analysis. Mean contraction frequencies were calculated for the 1-hr baseline, 3-hr treatment, and 3-hr post-treatment periods. The mean contraction frequency of each pair of *o,p'*-DDT-treated or control strips was averaged

over experimental runs to obtain a mean contraction frequency for each period and each treatment. The percentage increases cited in the text were based on contraction frequencies of *o,p'*-DDT-treated strips relative to control strips from the respective test period. To determine if the *o,p'*-DDT-treated strips differed from controls, we tested for the mean effect that the differences in mean contraction frequency between matched control and *o,p'*-DDT-treated strips equaled zero, the expected result if *o,p'*-DDT had no effect on contraction frequency (Winer, 1971). To determine dose and time effects as well as interaction between dose and time, the differences in mean contraction frequency between matched control and *o,p'*-DDT-treated strips were analyzed by repeated measures analysis of variance (ANOVA) followed by appropriate one-way ANOVAs (Winer, 1971). A separate repeated measures ANOVA was also performed on the control data, to ascertain if the solvent, ethanol, used to dissolve *o,p'*-DDT, had an independent effect. Posthoc comparisons of means were performed using the Student–Newman–Keuls method (Winer, 1971). An α level of 0.05 was assumed in all analyses.

RESULTS

The dose and time effects of *o,p'*-DDT on uterine contraction frequency are summarized in Fig. 1. During the treatment period, 10, 50, and 100 μM *o,p'*-DDT increased contraction frequency by 5, 23, and 66%, respectively, relative to controls; these differences were significant for the 50 and 100 μM *o,p'*-DDT-treated strips ($p < 0.05$). After removal of the test substance from the bathing medium, the contractions continued to increase during the post-treatment period, with concentrations of 50 and 100 μM *o,p'*-DDT increasing contraction frequency 39 and 104%, respectively, relative to controls ($p < 0.05$). Treatment with 10 μM *o,p'*-DDT decreased contraction frequency nonsignificantly by 0.3% relative to controls during the post-treatment period. No significant differences were detected between *o,p'*-DDT and control groups during the baseline period, as expected.

Analysis of the mean differences between *o,p'*-DDT-treated strips and matched controls showed that increases in contraction frequency were related to both dose and test period, with a significant interaction also observed (Fig. 1; ANOVA dose, time, and interaction effects, p

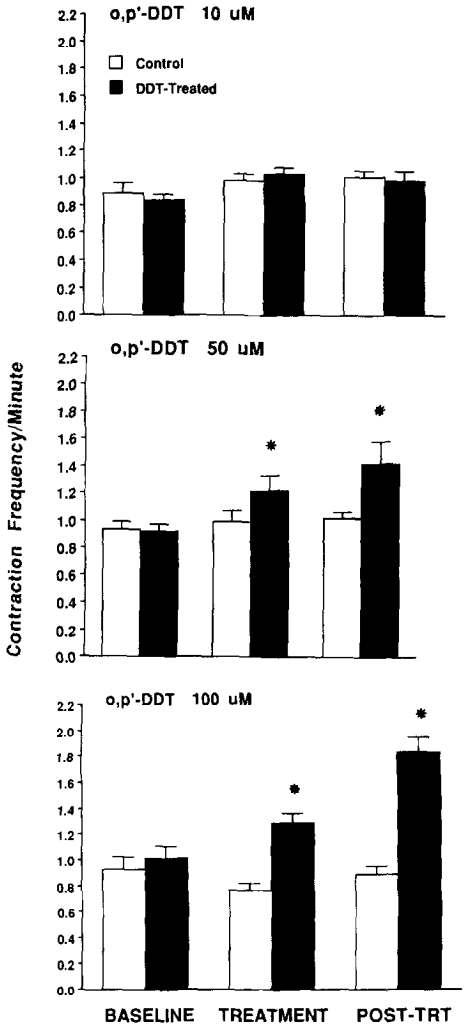

FIG. 1. Effect of *o,p'*-DDT on isometric contraction frequency in rat uterine strips treated *in vitro*. Each bar represents the mean ± SEM of six or seven animals. Asterisks (*) indicate groups significantly different from controls ($p < 0.05$).

< 0.001). No significant differences were observed between the dose groups during the baseline period, as expected. During the treatment period, only 100 μM *o,p'*-DDT increased contraction frequency significantly greater than the baseline value ($p < 0.05$). In the post-treatment period, the relative frequency of contraction continued to increase in uterine strips treated with either 50 or 100 μM *o,p'*-DDT, and was significantly greater than base-

line in both groups ($p < 0.05$), despite the absence of DDT in the bath. A dose effect was observed during the post-treatment period, with the relative increase in contraction frequency of strips treated with 100 μM *o,p'*-DDT greater than strips treated with 50 or 10 μM *o,p'*-DDT ($p < 0.05$). Additionally, during the treatment period, 100 μM *o,p'*-DDT elicited significant increases of contraction frequency compared to 10 μM *o,p'*-DDT ($p < 0.05$).

A representative polygraph tracing depicting the increased frequency in uterine strips treated with 100 μM *o,p'*-DDT is shown in Fig. 2. Although force was not statistically analyzed, 1.5–2.0 g of force per contraction was observed, with no apparent changes due to treatment or time in the muscle bath. Maximal contractile force, assessed prior to and after experimentation, exceeded 3.0 g in all preparations, indicating no loss of viability of the tissue.

Contraction frequencies of solvent controls for 10, 50, and 100 μM *o,p'*-DDT changed from baseline to treatment periods by +10, +6, and −17%, respectively (Fig. 1); however, this effect was not statistically significant.

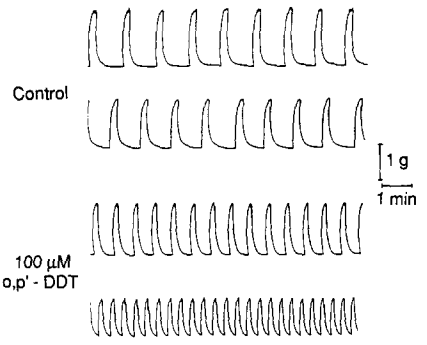

FIG. 2. Polygraph tracing showing the effect of 100 μM *o,p'*-DDT on rat uterine contraction frequency during the post-treatment period. The top two tracings are controls and the bottom two represent DDT-treated strips, all from the same animal. The duration of the period shown is 10 min.

DISCUSSION

Modulation of uterine contractility by certain pharmacological agents is well-established (Mehrotra *et al.*, 1985; Honnebier *et al.*, 1989; Swahn and Bygdeman, 1988; Schrock *et al.*, 1989; Tadmor *et al.*, 1990). However, the effects of environmental substances on smooth muscle excitation/contraction have received minimal attention. Despite evidence linking DDT exposure to preterm birth (Saxena *et al.*, 1980,1981; Wassermann *et al.*, 1982), this is the first demonstration that *o,p'*-DDT directly stimulates uterine contractility in a dose- and time-related manner.

Because contraction frequency increased with dose, the response was dependent on the amount of *o,p'*-DDT added to the muscle bath. The fact that no effect was observed in strips treated with 10 μM *o,p'*-DDT suggests that either a threshold exists for increased contraction frequency or that the techniques employed were insufficient to detect an observable response at this dose. It is notable that the frequency of contraction continued to increase in uterine strips treated with 50 and 100 μM *o,p'*-DDT even after removal of the compound from the bath. We suggest that either an appreciable amount of *o,p'*-DDT was retained by the tissue or that the DDT effect is not readily reversible. Because of DDT's lipophilicity, a significant amount may remain in the tissue following removal from the medium, consistent with *in vivo* data that indicate storage and bioaccumulation of such lipophilic compounds.

Unexpectedly, an inverse trend was observed between ethanol concentration and contraction frequency in the solvent controls. While not statistically significant, the decrease in contraction frequency observed in the controls for 100 μM *o,p'*-DDT may be due to ethanol inhibition of uterine contractility, since the phasic activity often ceased for a brief period of time following ethanol administration. Resumption of regular phasic activity, coupled with postexperiment assessment of maximal contractile force, suggests that the brief period of inactivity was not due to de-

creased tissue viability. Similar observations of the inhibitory effect of ethanol on myometrium have been reported both *in vivo* and *in vitro* (Wilson *et al.*, 1969; Lauersen *et al.*, 1981). The ethanol concentrations used in these experiments were determined by the solubility of *o,p'*-DDT and kept to a minimum. Because inhibition was not observed in *o,p'*-DDT-treated strips, *o,p'*-DDT may prevent or override any inhibitory action of ethanol.

While frequency of contraction is only one measure of contractility, this was the parameter most prominently affected by *o,p'*-DDT treatment. Occasionally, we observed that 100 μM *o,p'*-DDT initiated a change in the contractility pattern from increased regular contractions to one characterized by low-amplitude, high-frequency spike contractions. This may be significant, since studies with women (not exposed to DDT) suggest that a similar pattern is observed more often in women who subsequently deliver prematurely compared to those who deliver at term (Newman *et al.*, 1987).

Serum levels of DDT in women who develop preterm labor have been measured in the range of 0.1–0.6 μg/ml (Wassermann *et al.*, 1982; Saxena *et al.*, 1980,1981), while other studies have shown serum levels of exposed persons to be as high as 2.8 μg/ml (Kreiss *et al.*, 1981). These levels probably do not represent the total body burden of DDT, due to DDT's ability and preference to reside in lipophilic stores; in fact, adipose/serum ratios of 100–200 are not uncommon (Kreiss *et al.*, 1981; Polishuk *et al.*, 1970). While the effective concentrations in our investigation are somewhat higher than those typically found *in vivo,* DDT is likely to be better solubilized in serum and adipose tissue than in the saline buffer. The DDT concentrations in our study (3.5–35 μg/ml) are very similar to those effective levels in other studies which have used tissue and cell culture systems for investigation of DDT action (Price, 1978; Klaunig *et al.*, 1990; Warngard *et al.*, 1988).

DDT has cellular actions which could modify uterine contractility. For example, DDT decreases membrane potential in human liver cells (Schefczik and Buff, 1984) and retards sodium channel inactivation in insect nerve (Beeman, 1982). Other studies have demonstrated DDT inhibition of cellular calcium ATPases in lobster nerve (Ghiasuddin and Matsumura, 1981) and in human placenta (Treinen and Kulkarni, 1986), possibly resulting in altered cytosolic calcium. If such effects occurred in myometrium, the depolarization threshold of pacemaker cells could be lowered, increasing the rate of firing and resulting in increased contractility. Additionally, *o,p'*-DDT is an estrogenic isomer of DDT which interacts in a competitive manner with the rat uterine estrogen receptor (Welch *et al.*, 1969; Nelson, 1974). Estrogens have multiple effects on the uterus including stimulation of synthesis of the contractile proteins, actin and myosin, and increased gap junctional communication (Riemer and Roberts, 1986; MacKenzie *et al.*, 1983). If *o,p'*-DDT elicited either of these cellular responses in myometrium, improved propagation of action potentials and contractions could result.

In the present study, we have shown that *o,p'*-DDT significantly increased isometric contraction frequency in a dose- and time-related manner. While these results do not provide an explanation for the association between DDT and preterm birth, we suggest that the findings may be relevant since studies indicate that the frequency of uterine contractions is significantly greater in women who subsequently develop preterm labor compared to women who deliver at term (Katz *et al.*, 1986; Bell, 1983). In subsequent experiments, we have obtained similar results with *p,p'*-DDT, *p,p'*-DDD, and technical grade DDT (unpublished observations), and currently are examining a mechanistic basis for these findings.

ACKNOWLEDGMENTS

We thank Dr. Craig Harris for uterine tissue. This research was conducted as partial fulfillment of D.R.J.'s doctoral dissertation, and was supported, in part, with

predoctoral training grants to D.R.J. (NIH HD07048 and NIH GM07767) and research grants to R.L.C. (NIH ES04424) and R.C.W. (NIH HL27020). Additional support was provided by the Laboratory Animal and Data Analysis Cores of the P30 Center for the Study of Reproduction (NIH HD18258).

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