EFFECT OF SMALL DOSES OF ACTINOMYCIN D ON OESTROGEN-INDUCED UTERINE CHANGES IN THE IMMATURE RAT

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Actinomycin D has been intensively studied by a number of investigators interested in the inhibition of hormonal activity. These studies were recently reviewed by Samuels (1964) and Litwack & Kritchevsky (1964). It is generally agreed that this antibiotic acts by the inhibition of RNA synthesis and, more specifically, blockage of DNA-directed RNA synthesis. The doses of actinomycin D employed have generally been large enough to have toxic effects in addition to antagonizing hormonal action specifically. The effects of relatively low doses of actinomycin D upon oestrogen-induced uterine growth were examined in the present study.

Oestradiol benzoate, actinomycin D or both compounds in sesame oil were administered s.c. once daily for 4 consecutive days to dose groups of 20–35 immature (body weight 40–45 g.) female Sprague–Dawley rats obtained by caesarean section. On the 5th day the animals were killed, the uteri removed, weighed and quick-frozen. They were kept frozen until assayed for nucleic acids and for TPN-linked dehydrogenase activities (Hilf, Freeman, Michel & Borman, 1964). Nucleic acids were expressed as µg./mg. tissue and µg./uterus; enzyme activities were expressed as µm-TPNH produced/min./100 mg. tissue.

Table 1 summarizes the data pertaining to body weight, uterine weight and nucleic acids. Actinomycin D had no effect on uterine weight but decreased body weight at the highest dose studied. It reduced RNA concentration at two dose levels, but this effect was not dose-related. DNA was not affected, nor was the RNA:DNA ratio. Oestradiol benzoate induced a typical uterotrophic response, accompanied by a slight increase in RNA (both concentration and total) and a marked decrease in DNA concentration (but an increase in total DNA/uterus) resulting in a striking increase in the RNA:DNA ratio. Actinomycin D interfered with the oestrogen-induced uterotrophic response only at doses of the antibiotic which significantly reduced gain of body weight. Total RNA and DNA (but not concentration) decreased, reflecting the decrease in uterine weight. Oestrogen administration induced a significant increase ($P < 0.01$) in uterine glucose-6-phosphate dehydrogenase (control, $0.159 \pm 0.016$; oestradiol benzoate, $0.629 \pm 0.036$) and TPN-malic enzyme (control, $0.035 \pm 0.003$; oestradiol benzoate, $0.125 \pm 0.009$) activities, and actinomycin D did not alter the enzyme responses to oestrogen at any of the doses of antibiotic employed.

These results indicate that doses of actinomycin D which do not interfere with
normal body growth do not interfere with the uterotrophic response to oestrogen. Inhibition of oestrogen-induced uterine growth by dietary protein deprivation is similarly a reflection of untoward effects on the entire body (Lerner & Turkheimer, 1965). However, regression analyses on paired uterine and body weights at each dose level (groups 6–10) showed a highly significant lack of parallelism ($P < 0.01$), suggesting that the inhibition of the oestrogen-induced uterotrophic response was not due solely to the effect of this antibiotic on body weight. Caution is, therefore, indicated in the interpretation of data implicating specific inhibition of hormonal action when substances or procedures are used which may have generally toxic effects.

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REFERENCES


