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Response of female mice to anticonvulsants after pretreatment with sex steroids

We have examined in female mice the effects of lynestrenol (progestin) and mestranol (oestrogen) on the intensity and duration of activity of a series of anticonvulsant drugs.

Rumke & Noordhoek (1969) had shown previously that pretreatment of mice with large doses of lynestrenol (20 and 200 mg/kg) 48 h before receiving either phenytoin or phenobarbitone resulted in decreased protection against bemegride convulsions, and increased metabolism of the drugs. Banziger (1965), and Swinyard & Castellion (1966) have demonstrated that the minor tranquillizers chlordiazepoxide (Librium) and diazepam (Valium) in high doses protect mice from tonic extensor seizure produced by maximal electroshock. Chlordiazepoxide is rapidly and extensively metabolized in mice (Coutinho, Cheripko & Carbone, 1968) and its anticonvulsant activity pattern follows closely the disappearance rate of the parent drug and its major metabolites from the brain and plasma. Since both lynestrenol and mestranol have marked and opposite effects upon the metabolism of certain barbiturates (Blackham & Spencer, 1969) it occurred to us that these effects may also occur with phenobarbitone, phenytoin, chlordiazepoxide, and diazepam.

For each anticonvulsant studied 5 groups of 10 female TO mice, weighing 20–25 g, were pretreated with progestin (lynestrenol, 10 mg/kg), or oestrogen (mestranol, 1·0 mg/kg), or their oily vehicle, daily, for four days. On the fifth day, each of the 5 groups received an intraperitoneal injection of one of the following anticonvulsant drugs; phenytoin sodium, 20 mg/kg; phenobarbitone sodium, 40 mg/kg; chlordiazepoxide hydrochloride, 80 mg/kg; or diazepam, 20 mg/kg. At various times afterwards, they were subjected to maximum electroshock, using a shock of 70 V at 100 pulses/s (pulse-width 0·2 ms), for a duration of 0·3 s. This was delivered through silver ear electrodes, according to the method of Cashin & Jackson (1962). The current was supplied by a Scientific Research Instruments' square-wave stimulator. This shock produced tonic extensor convulsions in 100% of all animals not receiving anticonvulsant drugs; each mouse was tested once only.

Our results are summarized in Fig. 1. Lynestrenol produced a reduction in intensity and duration of activity with all of the anticonvulsant drugs examined, whilst mestranol had the reverse effect. Administration of the microsomal enzyme inhibitor SKF 525A mimicked the effect of mestranol, increasing the protection of mice receiving these anticonvulsant drugs. The observed changes in activity of the above anticonvulsant drugs may be due therefore to alterations in their rate of metabolism.

There may be however an alternative explanation. We have already shown that marginal but opposite changes in brain 5-hydroxytryptamine levels occur in female

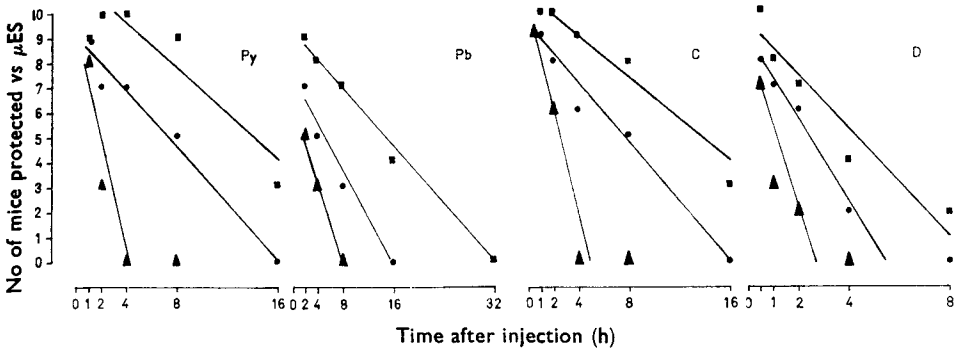

FIG. 1. Duration of action of four anticonvulsant drugs in female mice pretreated with oestrogen (■—■; mestranol, 1·0 mg/kg), progestin (▲—▲; lynestrenol, 10 mg/kg), or vehicle (●—●; controls, 0·1 ml/20 g) daily, subcutaneously, for four days. The anticonvulsant activity of phenobarbitone sodium (Pb; 40 mg/kg), phenytoin sodium (Py; 20 mg/kg), chlordiazepoxide HCl (C; 80 mg/kg) or diazepam (D; 20 mg/kg) was examined by maximal electroshock at various times after intraperitoneal injection.

mice pretreated with mestranol or lynestrenol (Blackham & Spencer, 1969). Schlesinger, Boggan & Griek (1968) showed that 5-hydroxytryptamine protected mice from electroshock seizures while reserpine pretreatment increased the animals' susceptibility to these seizures. Thus, whilst the changes in the response of these mice to anticonvulsant drugs may arise mainly from differences in their rates of metabolism, the changes possibly may be further influenced by differences in the susceptibility of the mice to the electroshock procedure, owing to changes in brain amine metabolism.

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