On the mechanism of tolerance to phenobarbitone: evidence against a role for enzyme induction

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It is frequently stated that tolerance develops to the central depressant action of phenobarbitone when it is given repeatedly to animals and man. However, the slow onset of the drug's effects makes quantitation of tolerance by techniques such as sleeping times very difficult. We have examined this problem with electronic activity monitoring, and now report on the rapid development of tolerance to the behavioural depressant action of phenobarbitone. The brain levels of phenobarbitone in acutely and chronically dosed animals have also been examined.

Female Wistar albino rats (body weight 180–220 g) were dosed with phenobarbitone (50 mg/kg i.p.) or equivalent volume of the vehicle (90% propane-1,2-diol i.p.) at 12 noon daily for 5 days. The animals were subjected to electronic activity monitoring as described by Sever, Caldwell & Williams (1976). Rats were monitored continuously for one day prior to the first injection to acclimatize them to the environment and then throughout the treatment period. Figure 1 shows the results after the first and last of 5 daily doses of phenobarbitone. In both cases, the activity of control animals showed a reproducible diurnal rhythm, which was altered by a single dose of phenobarbitone with a reduction in activity lasting for 16 hours. However, tolerance developed very rapidly to this behavioural depression, and after 5 doses, the activity of rats was not depressed by phenobarbitone. Indeed, at 12-16 h post injection the animals were hyperactive compared with controls, which may represent a withdrawal effect.

Although phenobarbitone is well-known to be a powerful inducer of microsomal drug metabolizing enzymes, we have shown that it does not alter its own metabolism when given chronically (Caldwell, Croft, Smith & Snedden, 1977) and that it accumulates in the tissues on repeated administration (Croft, Caldwell & Smith, 1978). Brain concentrations of phenobarbitone were examined over a period of 0-12 h after the administration of a single dose or the last of 5 daily doses of [^{14}C]-phenobarbitone (50 mg/kg; 10 μCi/animal, i.p.) and the results are shown in Figure 1. The brain levels of phenobarbitone in chronically treated animals were about twice those in those animals having only one dose, at all time points.

It is thus apparent that while tolerance develops to the behavioural depressant action of phenobarbitone, there is an increase in its brain levels. This indicates that an increase in the rate of metabolism and excretion of phenobarbitone as a result of enzyme induction is not responsible for the development of tolerance, and it is necessary to seek alternative explanations for this (see Caldwell & Sever, 1974).

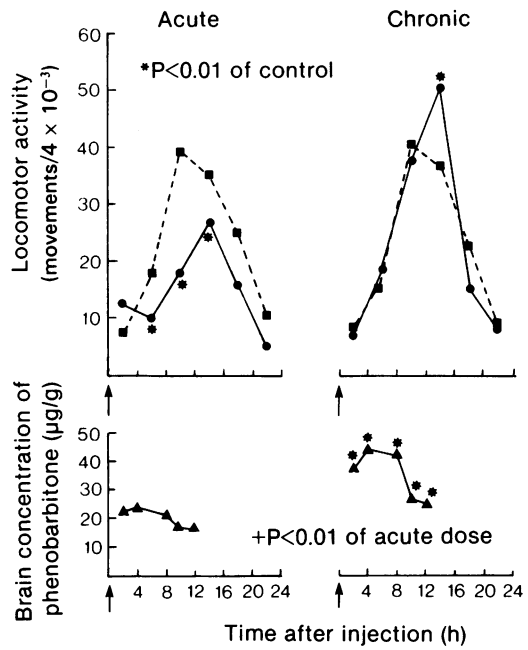

Figure 1 *Development of tolerance to phenobarbitone.*
The upper graphs show results of animal activity monitoring each point representing the mean result of at least 4 groups of 3 animals. The lower graphs indicate brain levels of phenobarbitone each point representing the mean result of 4 animals. Statistical analysis was by the Student *t* test. (■), control; (●), treated.

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