The influence of environmental temperature on the concentration of pentobarbitone in the liver and brain of rats

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Environmental temperature affects the body temperature of small laboratory animals. This influence is enhanced by the administration of narcotics, the animals becoming almost poikilothermic. In an earlier study, the body temperatures of guinea-pigs treated with barbiturates were found to fall in a cold and to rise in a hot environment. It was also found that the pentobarbitone but not barbitone concentrations in the tissues were correlated with the change in body temperature (Sotaniemi, 1967).

In the present study the effect of environmental temperature on body temperatures and tissue levels of pentobarbitone were examined in male rats treated with an intraperitoneal injection of pentobarbitone (30 mg/kg). The pentobarbitone concentration was determined according to Brodie, Burns, Mark, Lief, Bernstein & Papper (1953).

In the acute test, the body temperature was found to fall rapidly in a cold environment, while pentobarbitone concentrations in tissues remained at a higher level than those of the rats kept in a hot environment which showed a slight change in body temperature.

Pretreatment with phenobarbitone (80 mg/kg) for 48 hr reduced the fall in body temperature after pentobarbitone injection both in the animals kept at a cold and in those kept at room temperature. The pentobarbitone concentrations in tissues were lower than those of the corresponding control animals, which showed more pronounced changes in body temperatures.

Pretreatment with phenobarbitone for 4 weeks (40 mg/kg every fourth day) nullified the body temperature fall after pentobarbitone injection, and no undecomposed pentobarbitone was found in the tissues 2 hr after injection. In the corresponding control animals the body temperature fell for the first hour but regained its initial level within the second hour. The pentobarbitone concentrations in the tissues of the control animals were found to be lower than in the 48 hr experiment.

The results showed that environmental temperature definitely affected the body temperatures of rats treated with pentobarbitone. Heavy changes in body temperature retarded the fall of the pentobarbitone concentrations in the tissues. In rats pretreated with phenobarbitone the pentobarbitone disappeared more rapidly from the tissues and the change in body temperature was smaller.

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Hexobarbitone response in barbitone-dependent and withdrawn rats

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The response to a barbiturate often decreases with its repeated administration. Increased hepatic drug-metabolizing enzyme activity has been shown to be responsible for the

tolerance which rapidly develops to several barbiturates. A second type of tolerance, however, that caused by adaptation by cells of the central nervous system to the continuous presence of a drug, develops when certain barbiturates are given chronically at a sufficiently high dose level. Both mechanisms may contribute to the tolerance which is observed during chronic barbiturate administration. The present study was undertaken to provide information on the mechanisms underlying the changes in hexobarbitone response in barbitone-dependent and withdrawn rats.

Female Wistar rats, weighing approximately 50 g at the beginning of the experiment, were made dependent on barbitone sodium by the administration of up to 400 mg/kg per day in the drinking water for 32 days. At the end of this period, withdrawal—effected by replacing barbitone solution by tap-water—produced a withdrawal syndrome. At intervals during barbitone treatment and after withdrawal, the duration of anaesthesia following hexobarbitone sodium (150 mg/kg I.P.) was determined. At the same times the ability of liver microsomal preparations from treated and control animals to metabolize hexobarbitone *in vitro* was measured.

On each occasion, the hexobarbitone response appeared to correlate well with the hepatic drug-metabolizing enzyme activity. During the period of barbitone administration the animals were tolerant to hexobarbitone and the ability of liver preparations to oxidize hexobarbitone was increased. In addition, throughout this period there was no appreciable change in the extent of tolerance or degree of enzyme stimulation produced. Three weeks after withdrawal a hypersensitivity to hexobarbitone, associated with a decreased ability of liver preparations to oxidize hexobarbitone was found; both changes were still evident some 4 months later.

The results indicate that the altered hexobarbitone response occurring during barbitone administration and withdrawal may be explained in terms of altered liver drug-metabolizing enzyme activity. The possibility of drug treatment and/or withdrawal producing changes in the sensitivity of the central nervous system, however, must also be considered. The brain concentration of hexobarbitone at which animals awoke following injection of labelled hexobarbitone was therefore determined. During barbitone treatment, tolerant animals awake at lower brain concentrations of hexobarbitone. Further experiments to determine the significance of brain barbitone in these animals are at present under way.

Changes of the rat superior cervical ganglion induced by guanethidine (histology and cholinesterase histochemistry)

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Guanethidine is a sympathetic postganglionic neurone blocking agent, causing some depletion of noradrenaline. Prolonged treatment in rats causes a pronounced loss of specific and non-specific cholinesterase activity in sympathetic ganglia (Jensen-Holm & Zaimis, 1967; Jensen-Holm, 1967). In addition a considerable increase of proteins is found. The present investigation deals with the histochemical localization of cholinesterases and general histology of the rat superior cervical ganglion following treatment with guanethidine.

In some experiments unilateral preganglionic nerve division was undertaken in order to exclude centrally conditioned mechanisms. In other experiments unilateral post-