Potency of Barbiturates in Inhibition of Frog Gastric Secretion (36784)

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Previously Saidman *et al.* (1) found a correlation between anesthetic potency and the oil/gas partition coefficient. Their measure of potency was the MAC, *i.e.*, the minimum anesthetic concentration required to prevent a muscular response to a skin incision in 50% of the subjects to whom the anesthetic was administered. Schwartz and MacKrell (2) showed that the percentage of anesthetic needed to produce a given decrease in the H^+ secretory rate of frog gastric mucosa *in vitro* was proportional to the MAC in man and on this basis predicted the MAC values for chloroform and Compound 347 (Ethrane). These results suggested lipid solubility as a factor influencing the potency of anesthetics in inhibition of acid secretion.

In the work above (2) on frog gastric mucosa the anesthetics had molecules with no more than four carbon atoms. Mullins (3) points out that for compounds with more than four carbon atoms the anesthetic potency declines and that by the time one reaches a compound of C_{10} or C_{12} an anesthetic series is inert and higher analogues, whether they be alcohol, ether, or paraffin, have no anesthetic activity. Hence it is inferred that there is a site size limit for anesthetic molecules in biological membranes. In contrast, other investigators (4) found that the hypnotic activity of narcotics such as barbiturates was closely related to their relative lipophilic character as defined by the logarithm of the octanol–water partition coefficient, log *P*. Consequently, it was of interest to compare the behavior of barbiturates with anesthetics under similar conditions, namely, their effects on frog gastric mucosa. The question then is: to what extent is lipid solubility of barbiturates as defined by log *P* indicated as a factor in inhibition of acid secretion.

Methods. The experiments were performed on gastric mucosae of *Rana pipiens* with an *in vitro* method described in detail elsewhere (5). In this method each mucosa was mounted between cylindrical chambers. Two pairs of electrodes were used, one for sending current across the mucosa and the other for measuring the transmembrane potential difference (PD). The resistance was determined as the change in PD per unit of applied current. The nutrient bathing solution contained (m*M*): Na^+, 101; K^+, 4; Ca^{2+}, 1; Mg^{2+}, 0.8; Cl^-, 81; HCO_3^-, 25; phosphate, 1.0; and glucose, 10; and the secretory bathing solution: Na^+, 102; K^+, 4; Cl^-, 106. Both sides of the mucosa were gassed with 95% O_2 and 5% CO_2. The pH of the secretory solution was maintained at 4.90. After the control part of the experiment, barbiturate was added to the nutrient solution to yield 1 m*M* concentration in that solution. Preliminary experiments with concentrations in the nutrient solution varying from 0.1 to 5.0 m*M* indicated 1.0 m*M* as an optimal concentration for these studies.

Results. Figure 1 shows the effects of adding thiamylal (Surital) to the nutrient solution. At the time indicated by the arrow, thiamylal was added to a concentration of 1.0 m*M* in the nutrient solution. As with other inhibitory agents, the resistance increased and the H^+ secretory rate decreased. Here the resistance increased as much as 139% above control values and the H^+ rate decreased 83% below control values. The PD peaked and then decreased to some extent. Washing both sides with solutions without barbiturate restored the parameters to near control levels. Similar results were obtained with other barbiturates listed in Table I. For each barbiturate, nine separate experiments were performed at a concentration of 1 m*M* in the nutrient solution.

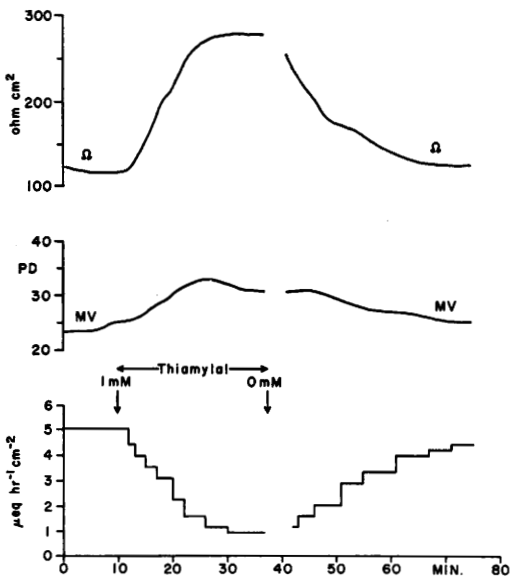

FIG. 1. Effects of thiamylal (Surital) on resistance, PD, and H^+ secretory rate in chloride solutions. The resistance, PD, and H^+ rate are plotted versus time. At the times indicated by the arrows the concentration of thiamylal in the nutrient solution was 1 m*M* and then decreased to zero.

In order to determine the potency of the barbiturates in the inhibition of acid secretion, the decrease in the H^+ secretory rate compared to control values just before the addition of barbiturate was determined in all cases during the 20–25 min interval following the addition of barbiturate to the nutrient solution. Table I gives the respective mean decreases in the H^+ rate during this interval together with their SEM values. The logarithm of the octanol–water partition coefficient, log *P*, as determined by Hansch, Steward and Anderson (4), was taken as a measure of lipid solubility. The log *P* of the barbiturates, as indicated in Table I, extended from 0.65 for barbital to 3.23 for thiamylal (4). As shown in Fig. 2, a plot of the decrease in H^+ rate was almost directly proportional to log *P*. Experiments were also performed with 1 m*M* thiopental. The point for thiopental is not plotted in Fig. 2 since, as expected, due to the partial precipitation of thiopental at 1 m*M* concentration in Ringer solution the point falls below the curve. For thiopental log *P* equals 3.00 and the mean decrease in H^+ rate at 1 m*M* concentration was 60%, comparable to secobarbital with a lower log *P* value.

TABLE I. Potency of Barbiturates in the Inhibition of the H^+ Secretory Rate in Frog Gastric Mucosa in Cl^- Solutions.

Barbiturate	log *P*	% Mean H^+ rate decrease
Barbital (Veronal)	0.65	14 ± 3[a]
Diallylbarbituric acid (Dial)	1.05	24 ± 5
Phenobarbital (Luminal)	1.42	38 ± 5
Pentobarbital (Nembutal)	1.95	48 ± 5
Secobarbital (Seconal)	2.15	59 ± 6
Thiamylal (Surital)	3.23	78 ± 6

[a] In each case this number denotes the mean decrease ± SEM.

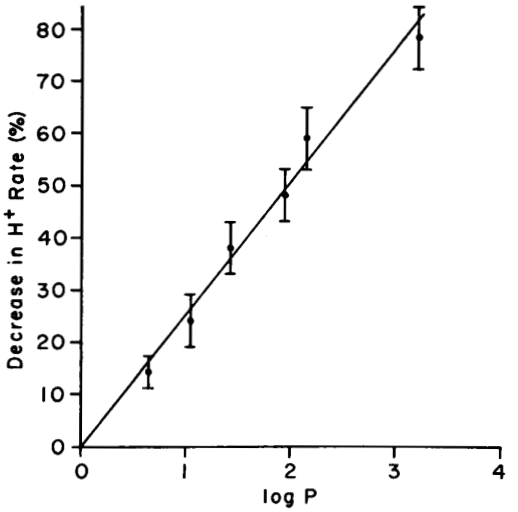

FIG. 2. Decrease in H^+ secretory rate (%) as a function of log *P*.

Discussion. The linear relationship suggests lipid solubility as a factor in the potency of barbiturates in the inhibition of acid secretion. Moreover, the inhibiting power of drugs on other systems such as the narcotic action on frog heart and muscle, bacterial luminescence, paramecium mobility, *etc.*, was dependent upon the lipophilic character of these drugs as determined by log *P* (6). Hansch and Anderson (6) remark on the overwhelming significance of log *P* as a

parameter. The present work lends support to the importance of this parameter.

The data can be regarded to a degree from a related viewpoint. It is known that lipid solubility for a chemical series as measured by partition coefficients increases within limits as the number of carbon atoms increases (3, 4). Barbiturates may be considered as belonging to different series in accordance with the R, R′ groups linked to the carbon atom of barbituric acid in the fifth position in the ring (4).

Lipid solubility as a factor in the potency of barbiturates implies that barbiturates penetrate at least to some extent into the lipid phase of membranes. The theory of Mullins with reference to a site size limit for anesthetics is not applicable to barbiturates, at least up to C_{12}. A recent suggestion attributes the activity of barbiturates to their disruption of the coenzyme flavine-adenine dinucleotide (7).

Conclusions. The decrease in H^+ secretory rate in frog gastric mucosa in chloride media was almost directly proportional to log P up to about an 80% decrease in the H^+ rate.

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