The lack of effect of ethanol ingestion on phenytoin half-life

Subject	No ethanol in blood $t_{1/2}$ (h)	Ethanol in blood $t_{1/2}$ (h)	
H.K.	12.0	13.5	n.s.
I.E.	6.3	4.3	n.s.
S.Y.	15.0	14.0	n.s.
D.S.	18.0	18.5	n.s.
I.B.	10.9	11.0	n.s.
	12.4 ± 4.4[a]	12.3 ± 5.2[a]	

[a] Mean ± SD. Half-life of phenytoin was determined from regression analysis of the linear part of the curve of log phenytoin concentration versus time in each subject. The regression lines were compared for slope and elevation in each subject with and without ethanol in blood. The difference was not significant at the 5% level for each subject.

administration of alcohol, served as control. The half-life of phenytoin determined in this study is in very good agreement with values reported recently[4]. The lack of effect of acute ethanol ingestion on the elimination of phenytoin from plasma may be due to two factors. The dose of phenytoin may have been too low to allow for inhibition of phenytoin metabolism to occur with concurrent administration of alcohol. In addition, the blood alcohol level also may have been too low or not been maintained long enough for induction of enzymes hydroxylating phenytoin.

In chronic alcoholic patients, the phenytoin half-life was found to be 16.3 h (SD ± 6.8) as compared to 23.5 h (SD ± 11) in a non-alcoholic control group[1]. In another investigation, 2.5 g/kg alcohol was given daily to 3 volunteers who had stable phenytoin levels[5]. No change occurred in 1 volunteer, in the second a decline, and in the 3rd a rise in the phenytoin plasma levels was seen.

The effect of ethanol on phenytoin metabolism appears complex, since it may either induce or inhibit the enzyme systems hydroxylating phenytoin. The resulting effect may depend on a balance of these antagonistic factors in a subject. A similar experience was made for the effect of ethanol on meprobamate metabolism in man[6].

Summary. Ingestion of ethanol, 1 g/kg, did not influence the phenytoin half-life in 5 volunteers after single i.v. administration of 3 mg/kg phenytoin. The control phenytoin half-life was 12.4 h (SD ± 4.4); with ethanol ingestion it was 12.3 h (SD ± 5.2).

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Variations of Cyclic Nucleotide Monophosphate Levels During Spontaneous Uterine Contractions

There is evidence suggesting that the effect of some smooth muscle relaxing drugs, β-adrenoceptor agonists and phosphodiesterase inhibitors, in several kinds of smooth muscle are mediated by cyclic AMP[1,2]. Contractions following stimulation of cholinergic receptors in intestinal muscle or α-adrenoceptors in vascular muscle have been reported to be associated with an initial reduction of the cyclic AMP level[1]. Smooth muscle contractions have also been found to be combined with an increase of the cyclic GMP level following stimulation of cholinergic receptors in intestine[3] and uterus[4]. The question may be raised whether corresponding changes of cyclic nucleotide levels occur during spontaneous rhythmic contractions and relaxations of smooth muscle. To investigate this problem, we have studied isolated rat uteri.

Uteri from rats weighing 200–250 g were dissected out and the horns were mounted in holders for recording of isometric tension. The rats had been injected with estradiol valerianate (100 µg/kg) or progesterone (4 mg/kg) s.c. for 1–3 days before sacrifice. The preparations were suspended in buffer solution (composition in m*M*) NaCl, 118.5; KCl, 4.7; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_2$, 23.8; KH_2PO_4, 1.2; glucose 5.5 at 37 °C and resting tension was adjusted to about 0.3 g. The solution was oxygenated by 95% O_2 + 5% CO_2. The muscles were equilibrated for about 1 h. At the end of the equilibration period, the spontaneous contractions had become regular. The duration of the contractions of estrogen-dominated uterus was usually about 30 sec, the frequency 1/min and the amplitude 2.7 ± 0.2 g. By the muscle-holders used in this experiment, the preparations could be instantly fixed during various stages of the contraction cycle. The freezing medium used for the fixation was frigen 12, cooled with dry ice (−70 °C). The frozen tissue was extracted with ice-cold 5% PCA. The two cyclic nucleotides were separated on AG-1-x8 formate (200–400 mesh) columns. After lyophilization the nucleotides were dissolved in sodium acetate and analyzed by the methods of GILMAN[5] and STEINER et al.[6] for the respectively nucleotides. Recoveries were usually 85–90% for cyclic AMP and 90–95% for cyclic GMP.

In a recent paper it was demonstrated that cyclic nucleotide concentrations varied during different stage of the estrus cycle[7]. In this study we have also found an effect of estrogen on cyclic GMP level. 20 h after injection

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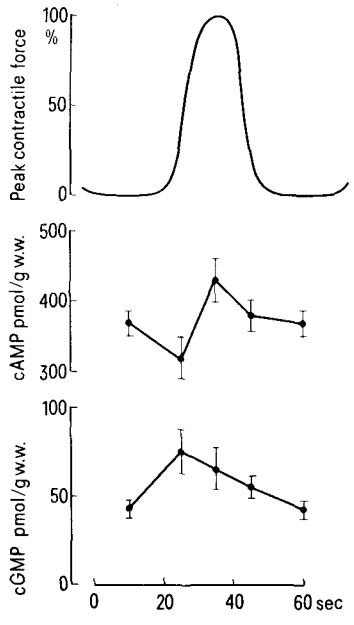
of estradiol valerianate, the cyclic GMP content of uterus horns was 149.2 ± 12.2 pmoles/g wet weight but, 68 h after injection, a value of 64.2 ± 10.5 pmoles/g wet weight (n = 8) was found. The difference was significant $p < 0.01$).

The results of the cyclic nucleotide determinations during the contraction cycle of estrogen dominated uterus are summarized in the Figure. The highest determined cyclic GMP level was found 5 sec after the start of the spontaneous contraction. At this time, the level was 30.6 ± 11.5 pmoles/g higher ($n = 8$, $p < 0.05$) than in the resting muscle. During the subsequent stages of contraction, the level fell towards the resting value. The cyclic AMP level reached its minimum level 321 pmoles/g 5 sec after the start of the contraction and its maximum 429 pmoles/g at the peak of contraction. The difference between the highest and the lowest cyclic AMP concentration (108 ± 35, $p < 0.05$) was probably significant.

In rats treated with progesterone (4 mg/kg) for 3 days before sacrifice, the spontaneous contractions of their uteri were small, 0.3–0.4 g, and the frequency was irregular. In these preparations it was not possible to follow the fluctuation of the cyclic nucleotides. The mean value of cyclic AMP for 8 animals was 370 ± 50 pmoles/g. The cyclic GMP level was 26 ± 2.5 pmoles/g, and significantly lower than in estrogen-dominated uteri.



Levels of cyclic AMP and cyclic GMP in rat uterus during different stages of a spontaneous contraction. Mean ± SEM of the results of 8–12 animals.

Our results demonstrate that during rhythmic contraction of rat uterus, oscillations in uterine concentrations of cyclic nucleotides occurred. This is in contrast to the report of DIAMOND and HARTLE[8]; these authors could not demonstrate significant fluctuations of cyclic nucleotides in rat uterus. However, when looking at their data the cyclic nucleotides tended to fluctuate in the same way as have been found in the present work, but the variations of their values were much larger than ours.

An interesting question is the causal relationship between the contraction-relaxation cycle and the observed changes of the cyclic nucleotide levels. In estrogen-dominated uterine muscle cells, the membrane potential is close to threshold for spontaneous discharge[9]. The rhythmic contractions have been suggested to be elicited by a synchronized discharge of actions potentials from the muscle cells[9]. The time-relationship between the electrical activity of the cell membrane and the changes of the cyclic nucleotides ought to be studied. If the electrical phenomena preceeds the nucleotide changes, the latter may be a consequence of the process of excitation.

It has been suggested that the spontaneous activity of uterus is associated with intramural generation of prostaglandins. Both these properties could be abolished by indomethacin[10]. Prostaglandins are also potent agents to increase the cyclic nucleotide levels in uteri[7]. The variations of the nucleotide levels as well as the electrical events in uterine muscle may therefore reflect prostaglandin generation.

Summary. Oscillations on the concentrations of cyclic nucleotides occurred during spontaneous rhythmic contractions in rat uterus. The levels of cyclic GMP and cyclic AMP were highest at the beginning of the contraction respectively the relaxation.

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Pathological Changes in the Liver of Mice Given 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin) is a potential contaminant of technical 2,4,5-trichlorophenol with a high toxicity for several species, including the rabbit[1], chicken[2,3], guinea-pig[3,4] and rat[3,4]. In all these species death occurs some time after administration of a single oral dose of dioxin. In the course of investigations[5] of biochemical changes in the liver of rodents, it was noticed that 7–10 days after dosing C57BL/6 mice the liver was pale and fatty. This communication describes studies arizing from this observation.

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