METABOLISM AND REGULATION II

Date : April 5, 1982
Title : HALOTHANE INHIBITS SYNTHESIS OF RETAINED AND SECRETED PROTEINS IN PERFUSED RAT LIVER
Authors : D. E. Rannels, Ph.D., K. E. Flaim, Ph.D. and L. S. Jefferson, Ph.D.
Affiliation: Departments of Physiology and Anesthesia, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033

Introduction. A normal balance of rates of protein synthesis (PS) and degradation is required for long-term maintenance of tissue function. Previous studies from this laboratory showed that exposure of lungs to halothane (HAL) disrupted this balance through a rapid, dose-dependent and reversible inhibition of protein synthesis, which was exerted at the cellular level (1). It was postulated that because of the lipophilic nature of anesthetic compounds, membrane-bound polysomes, synthesizing proteins destined for secretion, might be more susceptible to the inhibitory effects of HAL. Thus, the effects of HAL on synthesis and secretion of total plasma serum proteins and albumin (ALB), as well as the synthesis of retained liver proteins, were investigated.

Methods. Liver perfusion, analysis of polysome aggregation, and estimates of whole liver protein and ALB synthesis were as detailed earlier (2). Total PS was measured in acid precipitable [14C]leucine-labeled ALB in the perfusate.

Results. Pre-exposure of perfused liver to HAL (4%) for 15 min inhibited PS by 20% (p < 0.05). Relative rates of ALB synthesis were unchanged in HAL-exposed tissues (control, 11.1 ± 0.4; HAL, 11.0 ± 0.5% of total protein), suggesting that synthesis of retained liver proteins and of secretory proteins were affected equally. The inhibition of PS was accompanied by a 30% increase in the RNA content of ribosomal subunit peaks isolated by sucrose gradient centrifugation, suggesting inhibition of peptide-chain initiation by the anesthetic. In 2 h perfusions, HAL reduced retained PS 30%. The time course of secretion of newly-synthesized protein into the perfusate remained linear in the presence of the anesthetic, but the rate of secretion was reduced 40% (Figure 1), reflecting the reduction in PS. Secretion time was not altered by HAL exposure (control, 39 ± 1 min; HAL, 42 ± 2 min). Similar observations were made when secretion of newly-synthesized ALB was monitored.

Discussion. The present studies show that HAL rapidly inhibits synthesis of liver proteins, but suggest that membrane-bound polysomes are not affected preferentially as compared to free polysomes. The effect of HAL appears to involve inhibition of the initiation of polypeptide synthesis, rather than of polypeptide chain elongation. Reversibility of this inhibition has not been investigated as yet, but the effects of similar doses of the anesthetic were rapidly reversed in lung tissue (1). Inhibition of total protein and ALB secretion may reflect the overall inhibition of synthesis of total (retained + secreted) liver proteins, rather than inhibition of the secretory process itself. This hypothesis requires further investigation, but is supported by the lack of an effect of HAL on secretion time. Conclusions pertaining to the clinical relevance of this inhibition may await more extensive studies of the dose-response curves and the reversibility of the effect, although the inhibitory effects of HAL are of interest in regard to continued normal metabolic function in anesthetic-exposed tissues.

References.

Acknowledgements. This work was supported by grants HL-20344, HL-00294 and AM-13499 from the N.I.H. The authors thank Bonnie Merlino for secretarial assistance.

Figure 1. Accumulation of total secreted protein in the perfusate was monitored with time + HAL exposure. Livers were exposed to HAL for 20 min prior to the beginning of the time course shown.