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TITLE: INFLUENCE OF HALOTHANE AND DIETHYL ETHER ON THE DECAY OF THE POTENTIATED STATE IN MAMMALIAN MYOCARDIUM

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Introduction. The mechanism underlying the negative inotropic action of potent general anesthetics is incompletely understood. Previous studies have suggested that anesthetics exert effects on contractile proteins, on the cardiac cell membrane, and on intracellular membraneous storage depots for calcium (1). The relative importance of these various sites is not known. Bass (2) has shown that observation of the effects of various interventions on retention of the potentiated state in heart muscle can reveal information about the internal stores of $Ca^{++}$ which play an important role in cardiac electromechanical coupling. In the present study, the effect of halothane and ether on memory for the potentiated state in cat papillary muscle has been determined in an effort to better characterize the mechanism underlying the negative inotropism displayed by these anesthetics.

Methods. Kitten right ventricular papillary muscles were suspended in Krebs-Henseleit solution equilibrated with 95% $O_2$-5% $CO_2$ and held at a constant temperature of 25C. The muscles were contracted isometrically at a rate of 16 per minute for a period of 45 minutes to insure stability. Stimuli at a strength of 1.5 threshold were applied via silver-silver chloride field electrods. A potentiated state was induced in the muscles by paired-pulse stimulation (method of post-extrasystolic potentiation). Following the attainment of a stable potentiated state, paired stimulation was abruptly stopped and single pulse stimulation was resumed following rest periods of 1,2, and 3 minutes. Using this maneuver it was possible to determine the time course of decay of (or the loss of memory for) the potentiated state which had been produced by the paired-pulse stimulation. After control measurements were obtained the Krebs-Henseleit bathing solution was equilibrated with0.7 and 1.5 volume per cent halothane or with 2.0 and 4.0 volume per cent ether, i.e., each muscle was exposed serially to two concentrations of only one anesthetic. The time course of decay of the potentiated state was then determined in the presence of these anesthetics for comparison with control values.

Results. Both halothane and ether caused dose related, statistically significant increases in the rate of decay of the potentiated state. Under all conditions tested, paired pulse stimulation caused at least a doubling of developed force. Halothane and ether caused significant decreases in force development during both single and paired pulse stimulation. Data for both anesthetics are presented in table 1 and 2.

Table 1 Halothane

| n=5 | Force (g) | | %Decrease in PS at: | | |
|---|---|---|---|---|---|
| | SP | PS | 1 min. | 2 min. | 3 min. |
| Control | 2.01 | 4.09 | -16 | -25 | -40 |
| Hal. 0.7% | 1.04 | 2.07 | -25* | -44# | -65 |
| Hal. 0.5% | 0.76 | 1.78 | -33* | -41* | -63# |

Table 2 Ether

| n=5 | Force (g) | | %Decrease in PS at: | | |
|---|---|---|---|---|---|
| | SP | PS | 1 min. | 2 min. | 3 min. |
| Control | 1.37 | 4.15 | -6 | -25 | -42 |
| Ether 2.0% | 1.02 | 3.67 | -15* | -42* | -56* |
| Ether 4.0% | 0.81 | 2.92 | -25* | -51* | -67* |

SP=Single pulse stimulation
PS=Paired pulse stimulation. (Potentiated state)
*p<0.02, #p<0.05 (Significance of difference from control % decrease)

Discussion. Experiments similar to these, but dealing with agents known to modify transmembrane $Ca^{++}$ flux, have been performed by Bass(2) whose observations support to the hypothesis that the $Ca^{++}$ influx occurring during depolarization, while not immediately responsible for determining the strength of mammalian myocardial contraction, serves to load intracellular $Ca^{++}$ storage sites. The force of contraction is controlled mainly by $Ca^{++}$ released from these storage sites and appears to depend upon the content of $Ca^{++}$ within these sites. Bass found that agents which release $Ca^{++}$ from internal stores greatly accelerate the decay of the potentiated state. Conversely, low extracellular sodium, which inhibits $Ca^{++}$ efflux from the cell, greatly prolongs the memory for the potentiated state and, at the same time, causes a positive inotropic effect. It is postulated that the halothane induced loss of memory for the potentiated state shown here is related to an increased efflux of $Ca^{++}$ from the myocardial cell which is associated with a decreased sequestering of $Ca^{++}$ by internal storage sites. This results, secondarily, in a decrease of the force of myocardial contraction.

REFERENCES.

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2) Bass, O: The decay of the potentiated state in sheep and calf ventricular myocardial fibers. Circ. Res. 39:396-399, 1976.