TITLE: SOME EFFECTS OF HALOTHANE AND ISOFLURANE ON ACETYLCHOLINE ACTIVATED ION CHANNELS

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Introduction. After 120 years of use the mode of action of general anesthetics is still incompletely understood. One of the most commonly accepted theories of anesthetic action involves the drugs' interaction with the lipid layer of the cell membrane. In this study this interaction was observed by evaluating the effects of anesthetics on the acetylcholine activated ion channel at the neuromuscular junction. This evaluation was performed by observing the effects of anesthetics on miniature endplate currents (MEPC).

Methods. The effects of halothane and isoflurane on miniature end plate currents (MEPC')s were evaluated. All studies were performed using the in vitro frog sartorius muscle preparation at a temperature of 19-21°C. The muscle was mounted in a plexiglass bath (volume 2ml) and constantly perfused with Ringer's solution modified for the amphibian (flow rate 4ml/min). After control measurements were made, the muscle was perfused with anesthetic containing Ringer solution for a minimum of 10 min. Anesthetic was added to the solution by passing compressed air through a calibrated vaporizer, the output of which was bubbled through the anesthetic containing Ringer bottle. At the end of each experiment a sample of solution was withdrawn from the bath and analyzed for anesthetic content by gas-liquid chromatography. MEPC's were recorded using the 2 electrode voltage clamp technique of Dionne and Stevens[1] (obtained from WPI/Inc.). In this technique two electrodes, one to record membrane potential changes and the other to pass current of opposite polarity into the cell, are inserted in close proximity to the endplate region of a cell. The feed back circuit has a sufficiently fast response time so that, under satisfactory circumstances, no alteration of membrane potential is seen while the MEPC is recorded. Recordings were considered satisfactory if the growth phase of the MEPC was 0.5 msec or less. Ten MEPC's were recorded at each four clamped membrane potential (80, 90, 100 and 120 mv) before and after application of each concentration of anesthetic being studied. MEPC's were isolated using a window discriminator and recorded on floppy disk for later analysis. MEPC's were analyzed for amplitude and time constant of decay of the MEPC (τ_D). τ_D gives an estimate of mean ion channel opentime.

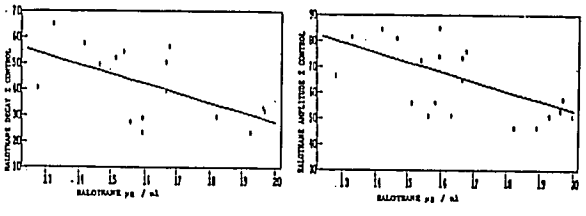
Results. Both halothane and isoflurane produced dose related decreases in MEPC amplitude and τ_D (Figs 1, 2). At no time was an increase in τ_D seen as has been reported by others. Neither anesthetic altered the normal potential related increase in either MEPC amplitude or τ_D. At the higher concentrations studied halothane and, to some extent, isoflurance caused the normally monoexponential decay curve to take on a biexponential character.

Discussion. Though the mode of action of general anesthetics is still not understood, the observation of the decrease in mean channel opentime was evidenced by the decreased τ_D suggests strongly that general anesthetics "fluidize" the membrane lipid making it more difficult for the channel to maintain the open state. Thus anesthetics would tend to interfere with cell to cell transmission. This may be part of the mechanism of general anesthesia. It may also be the avenue of the mechanism whereby anesthetics potentiate the actions of nondepolarizing muscle relaxants.

References

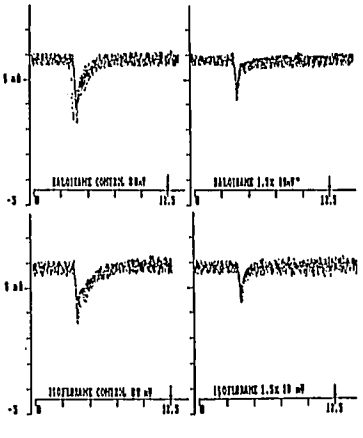
1. Dionne, V.E. and Stevens, C.F. J Physiol 251:245, 1975.

Figure 1



Effect of halothane on MEPC amplitude and time constant of decay.

Figure 2



Examples of MEPC's before and after halothane and isoflurane. Each figure is 10 superimposed traces.