Cells were labelled with [3H] inositol for 24 hours and treated with 10 nM ET for 1 minute. ET significantly stimulated the production of InsP, Ins(1,4)P_2, Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 reaching about 2-fold above control for Ins(1,4)P_2 and Ins(1,4,5)P_3 measured by HPLC. When cells were pretreated with ISO for 10 minutes and then stimulated by the same dose of ET, the production of each isomer of inositol phosphates was reduced. However, ISO did not alter the basal levels of inositol phosphates. In addition, when inositol phosphates were measured after 10 minutes of incubation with increasing concentrations of ET, ISO was found to inhibit the sustained formation of total inositol phosphates. In these experiments it appears that the maximum level of stimulation was decreased while the EC50 was not altered. This suggests that ISO may regulate ET-induced inositol phosphate formation by a mechanism beyond the receptor.

To investigate this possibility, we have further investigated the effect of forskolin, a direct agonist of adenylate cyclase, on ET-induced inositol phosphate formation. It was found that forskolin mimicked the inhibitory effect of ISO on ET-stimulated inositol phosphate formation. Finally, when cells were treated with ISO or forskolin, the production of intracellular cAMP increased by 14-fold in ISO-treated and 11-fold in forskolin-treated cells when compared to control cells. The effect of ISO was totally reversed by the non-selective β-adrenergic receptor antagonist, propranolol. These results suggest the idea that the inhibitory effect of ISO on ET-mediated inositol phosphate formation may be regulated by a cAMP-dependent mechanism.


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Title: Memory Evanesence In Mice Exposed To Halothane
Author: E Rosman MD, D Quartenmain PhD, H Turnford MD
Affiliation: Departments of Anesthesiology and Neurology, New York University Medical Center, New York, NY 10016

Introduction: Inhalational anesthetics affect memory. Antegrade amnesia has been demonstrated with halothane using an animal model of inhibitory passive avoidance learning.1 This study examines the amnesic effects of halothane as a function of time.

Method: After institutional approval, 80 adult Swiss-Webster mice (25-35 gm) were studied. Prior to training, half were exposed to air (A) and half to halothane (H). Mice were anesthetized for 30 mins in a 5L chamber into which 2% halothane in O_2 flowed at 6 L/min. Sodas lime was placed under the a perforated plate in the chamber. Training of H mice began 15 mins after return of ambulation. A and H were trained in a two-compartment (dark and illuminated) shuttle chamber. Each mouse was placed in the illuminated side and a door opened, allowing passage to the dark side where a 0.2 mA shock was administered for 0.1 sec. Initial training latencies were compared between A and H to accept adequate locomotor recovery. A and H, divided into 4 subgroups, were tested in the shuttle chamber at 1, 3, 7 and 10 days after training (n=10).

Memory of shock retention was ascertained by measuring crossover from illuminated to dark side (testing latency) with maximal score of 300 sec. Data analyzed using two-way ANOVA and Student-Newman Keuls test.

Results: No significant difference occurred between training latencies of A and H. Results are summarized in Fig 1. H test latencies were significantly less than A at all times. There was a significant effect of the time of testing where test day 3 latency was greater than any other day within the H group (p<.05).

Discussion: Exposure to halothane had an amnesic effect on day 1 probably due to retrieval failure. This is supported by the improved memory seen on day 3. Shock memory declined on days 7 and 10. Scopolamine has a similar qualitative temporal decrement on memory retention.2 In undrugged, memory improvement with time has been demonstrated using active avoidance learning.3 It is possible that after normal learning, increasing sensitivity to neurotransmitters occurs at specific synapses. With time, sensitivity declines and leads to forgetting.4 Halothane exposure prior to training may interfere with memory consolidation and produce a weakened memory trace which temporally improves as a result of the transiently increased synaptic sensitivity, then declines as this effect wanes.

References:
2. Behav Neural Biol 50:300-310, 1988

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Fig 1. Test latencies when mice are exposed to air or halothane prior to training.