

Title: HALOTHANE INDUCES DEPRESSOR RESPONSES TO NOXIOUS STIMULI IN THE RAT.

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INTRODUCTION: Although the effects of inhalational anesthetic agents on reflex movement (MAC) and heart rate responses to noxious stimuli have been studied in several species, little attention has been paid to the effect these agents have on the blood pressure responses to the noxious stimuli used. We examined the effect of increasing concentrations of halothane on the blood pressure response to various standardized noxious stimuli in the rat.

METHODS: Male Sprague Dawley rats weighing 584 ± 24 g (mean \pm s.e.m., range 498 - 700, n=9) were anesthetized with 2% halothane (H) in an induction chamber. After tracheostomy, mechanical ventilation was instituted to maintain the end-tidal (F_{ET}) CO_2 concentration at $5.0 \pm 0.5\%$. Rectal temperature was servo controlled at $36-37^\circ C$. The right carotid artery and jugular vein pressures were transduced. As pilot studies had demonstrated depressor responses to certain noxious stimuli, bilateral vagotomy was performed to prevent vagal influences. Systolic, diastolic and mean arterial pressures (MAP), heart rate (HR) and central venous pressure (CVP) were continuously recorded. $F_{ET}CO_2$ and $F_{ET}H$ were monitored by mass spectroscopy. After 30 minutes of equilibration at an $F_{ET}H$ of 0.75%, noxious stimuli were applied at five different sites in random order (base of tail; mid-portion of tail; tip of tail; hindlimb footpad; forelimb footpad). Stimuli to the tail were applied by an 8" rubber shod tubing clamp and stimuli to the footpads were applied using a 5" hemostat. Each stimulus was applied for 60 s and the responses measured were the maximum changes in MAP, HR and CVP during the period of stimulation. MAP was allowed to stabilize between stimuli. After 15 minutes equilibration at each new concentration, the five stimuli were repeated at $F_{ET}H$ of 1.0%, 1.25%, 1.5%, 1.75% and 2.0%. The MAP responses at $F_{ET}H$ of 1.0% or greater were compared to the responses at $F_{ET}H$ of 0.75% using a paired 't' test, with $\alpha=0.05$.

RESULTS: Clamping the base of the tail (BT) at $F_{ET}H$ of 0.75% caused a pressor MAP response in 7 out of the 9 rats; the response at this anesthetic concentration was considered the "control". At $F_{ET}H$ of 1.0% or greater the responses were almost exclusively depressor (Fig.). P values are displayed on the figure. The MAP responses at other sites of stimulation were more variable, but still displayed frequent depressor responses as observed with BT clamp. There was a positive correlation between MAP responses and HR responses to BT clamp ($r=0.68$). However, depressor responses were not associated with changes in CVP. Atropine $0.1-0.2$ mg·kg⁻¹ i.v. was administered to 4 rats but did not block the depressor response. In 4 rats the $F_{ET}H$ was reduced back to 0.75% with restoration of the pressor responses to BT clamp. Additional studies were performed as follows: In 2 rats, pithing the brain, but leaving the spinal cord intact, abolished the depressor response to BT clamp. In 4 rats aortic flow was measured, and at $F_{ET}H$ of 1.25%, BT clamp produced decreases in cardiac output (CO) of $16.1\% \pm 5.7\%$ (mean \pm s.e.m.) and systemic vascular resistance (SVR) of $17.6\% \pm 7.1\%$ (mean \pm s.e.m.).

DISCUSSION: Our results demonstrate that increasing $F_{ET}H$ from sub-MAC levels to MAC levels or greater causes a statistically significant reversal of the blood pressure response to a standard noxious stimulus from a pressor response to a depressor response. This effect is consistently demonstrated, especially by stimuli to the base of the tail, and is reversible with H washout.

Variable blood pressure responses to noxious stimuli have been previously observed in the rat and other animals but have not been fully evaluated¹. The mechanism of the depressor response is unclear but appears to be due to a central effect of H. It is not cholinergically mediated, and is not related to changes in CVP. The correlation with the decrease in HR, and the observations of concurrent falls in both CO and SVR, all suggest that withdrawal of sympathetic tone is producing the fall in MAP. However, active mechanisms may be contributing to the vasodilatation and need to be excluded². This rat model may be useful to further examine mechanisms whereby H modifies the hemodynamic responses to noxious stimuli and also to examine mechanisms of passive or active vasodilatation with anesthetics. An important implication of our findings is that previous determinations of anesthetic potency in the rat may have been confounded by large and unrecognized decreases in blood pressure (up to -80 mm Hg from baseline). Furthermore, HR changes in response to noxious stimuli which have been reported in the rat³, may have been, in part, reflex increases secondary to major falls in MAP. All investigators using rats or other laboratory animals should be aware of possible anesthetic induced depressor responses to their interventions, which will not be evident unless blood pressure is monitored.

REFERENCES: 1. McLennan H. On the response of the vasomotor system to somatic afferent nerve stimulation, and the effects of anaesthesia and curare thereon. *Pflugers Archiv* 273:604-613,1961

2. Ross G. The regional circulation. *Ann Rev Physiol* 33:445-478,1971

3. Kissin I, Morgan P, Smith L: Anesthetic potencies of isoflurane, halothane, and diethyl ether for various end-points of anesthesia. *Anesthesiology* 58:88-92,1983

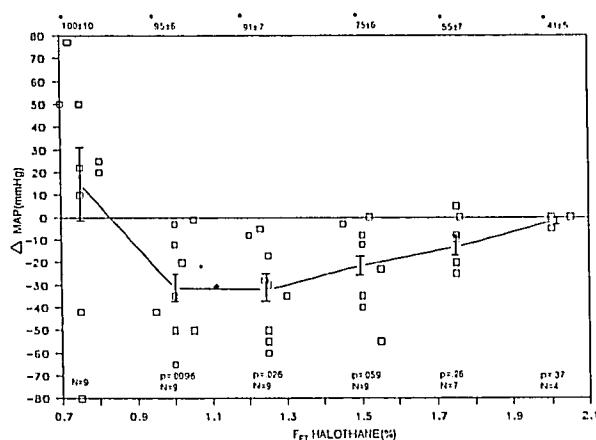


Figure. Maximum change in mean arterial pressure (MAP) in response to base of tail clamp with increasing end-tidal concentrations of halothane. Blocks represent individual observations. Bars indicate the standard error centered on the mean at each $F_{ET}H$. * MAP pre-stimulus (mean \pm s.e.m.) at each $F_{ET}H$.