Effects of Intravenously Administered Lidocaine on Pulmonary Vagal Afferents and Phrenic Nerve Activity in Cats

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The ability of lidocaine to suppress activity of single vagal afferent fiber and that of phrenic nerve was studied in 20 cats anesthetized with pentobarbital. Slowly adapting stretch receptors (SAR, n=16) and rapidly adapting stretch receptors (RAR, n=7) were identified by their discharge pattern to pulmonary inflation. Intravenous lidocaine (1 $mg \cdot kg^{-1}$ or 2 $mg \cdot kg^{-1}$) produced a suppression of SAR activity but not of RAR activity. Suppression of phrenic nerve activity lasted much longer than that of SAR. These findings indicate that iv lidocaine acts more dominantly on CNS than on peripherals. We conclude that iv lidocaine prevents cough and hemodynamic changes caused by airway manipulation mainly through its action on CNS and not on peripherals (peripheral nerves or their receptor). (Key words: airway reflex, local anesthetics, lidocaine, phrenic nerve, vagus, pulmonary afferent fiber)

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The intravenous administration of lidocaine is common in clinical practice to attenuate increases in heart rate, arterial blood pressure and intracranial pressure during airway manipulation[1–4]. Until recently, there were few reports suggesting how lidocaine might affect the reflex arc associated with airway stimulation. Systemically administered lidocaine has been shown to have an effect on the CNS. Jolly, et al.[5] demonstrated that lidocaine supresses brain-stem function and Dohi, et al.[6] reported suppression of dorsal horn nociceptive neurons by iv lidocaine. However, it is also obvious that iv local anesthetics have an effect on conduction in small fibers as well as by influencing the CNS. To examine this possibility, we evaluated the effects of intravenous lidocaine (1 and 2 $mg \cdot kg^{-1}$) on single pulmonary vagal afferent fibers. In additional experiments, we examined the effect of iv lidocaine on phrenic nerve activity in order to compare that effect with the effect on vagal afferents in the same preparation.

Methods

Experiments were conducted on 20 cats of either sex weighing 2.0–4.2 kg. Animals were initially anesthetized with a halothane-oxygen combination.

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Following the cannulation of a femoral vein (for fluid administration), femoral artery (for blood pressure monitoring and blood gas analysis) and tracheal intubation, the animals were paralyzed with pancuronium and mechanically ventilated with 100% oxygen. Halothane was discontinued and an anesthetic state was subsequently maintained by intermittent sodium pentobarbital injection for the remainder of the experiment (initial dose 8 $mg \cdot kg^{-1}$ iv, supplemented with 4 $mg \cdot kg^{-1}$ dose as necessary). Total dose of sodium pentobarbital during the experiment was 48–64 $mg \cdot kg^{-1}$.

Arterial blood pressure was continuously monitored and maintained within normal limits. Body temperature was measured via an esophagealthermister and maintained near 37°C with the use of a heating pad and an infrared heating lamp. Ringer's solution was infused intravenously throughout the experiment to maintain hydration.

The left vagus nerve was exposed in the neck and cut to insure that by placing the recording electrode on distal end of the nerve recordings were made only from afferent fibers. The skin around the exposure site was mounted on a metal ring forming a well over the exposed nerve. Parafilm was placed beneath the nerve to shield it from the surrounding tissue. Mineral oil, warmed to 37°C, was then placed in the well to protect the nerve from cooling and drying. Recordings were made with silver electrodes from thin filaments of the nerve prepared by dissecting the distal end of the cut nerve under microscopic control. Filaments from the nerve were progressively divided until single unit activity could be distinguished from all other activity by differences in spike size. Electrical activity was monitored on an oscilloscope (DISA 2000 C) throughout the experiment. The unit activity was also stored on a tape recorder for retrospective analysis.

Vagal afferents arising from the lung and lower airways were divided into two separate groups (SARs: slowly adapting mechanoreceptors and RARs: rapidly adapting mechanoreceptors) according to their discharge pattern to pulmonary inflation by a mechanical ventilator (Shinano Seisakusho SN 480-5) which allowed us to increase or decrease tidal volume and respiratory rate. In each experiment, we tried to determine the receptive fields of these afferents by stimulating the lung with glass probes through the opened thorax. Tracheal pressure was continuously monitored with a pressure transducer (Statham P23D) connected to a sidearm of the tracheal tube. End-tidal CO_2 was also monitored throughout the experiment with an infrared CO_2 analyzer (Datex). Conduction velocities of these afferents were calculated by the pretriggering averaging method.

In three cats, the C5 branch of the left phrenic nerve was also isolated at the neck and the distal end of the cut nerve was mounted on unipolar silver wire electrodes. Phrenic nerve compound action potentials were recorded simultaneously with the unit activity of the vagal afferents.

In both series of the experiments, following baseline recordings, lidocaine 1 or 2 $mg \cdot kg^{-1}$ was administered intravenously and drug effects were subsequently observed on neuronal activity. The bolus injection of lidocaine was chosen because that is closer to how it would be given clinically.

Results

Electrical signs of activity in each single pulmonary vagal afferent were easily identified by the unit's response to pulmonary inflation. The firing patterns were associated with activity in two receptor types, slowly adapting stretch receptors (SAR, n=16) and rapidly adapting stretch receptors

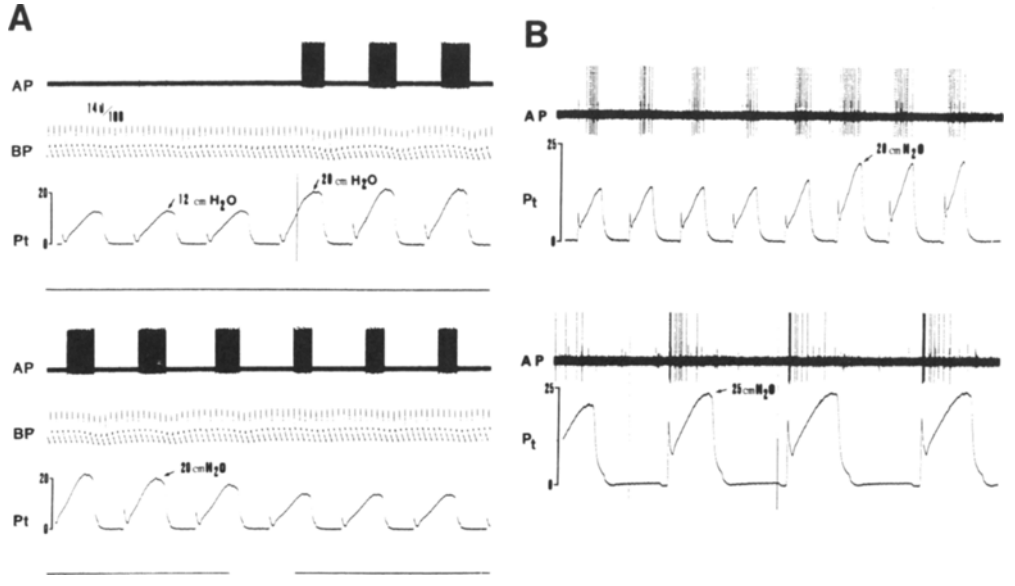

Fig. 1. A typical response of an SAR and RAR. (A) An SAR was silent until tracheal pressure (Pt) exceeded about 12 cmH_2O. Responding to an increase in Pt, this unit began to fire. The period of inflation for this unit was kept constant. Note that when Pt decreased gradually, a number of discharges per single pulmonary inflation also decreased. (B) The discharge pattern of an RAR was shown when the peak tracheal pressure and the inflation period were altered. Note the rapid rate of adaptation to maintained inflation and its more irregular pattern of discharge. These characteristics enabled us to distinguish an RAR from an SAR. AP; action potentials, BP; arterial blood pressure, Pt; tracheal pressure.

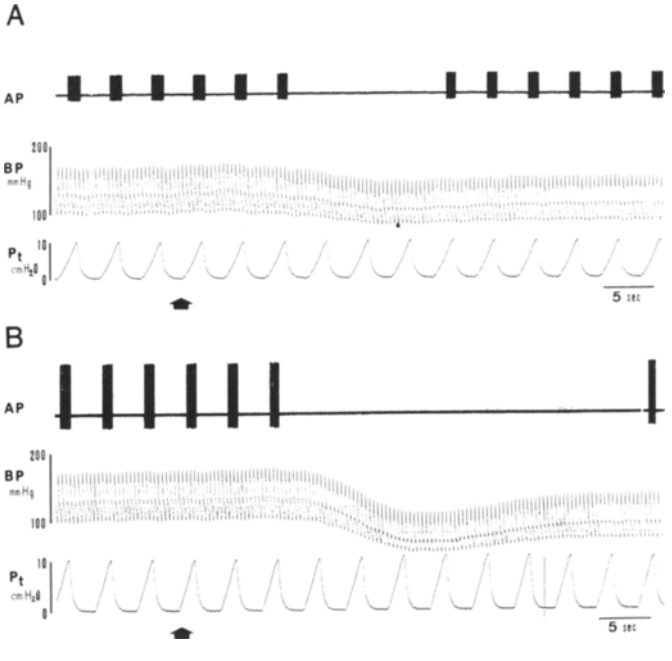

Fig. 2. Response of an SAR to lidocaine (1 $mg \cdot kg^{-1}$ in A, 2 $mg \cdot kg^{-1}$ in B) in an open-chest artificially ventilated cat. The nerve endings was located in the left lung. Lidocaine was injected at the arrow. Note that lidocaine produced a complete suppression of SAR activity, which was longer lasting following the 2 $mg \cdot kg^{-1}$ dose than 1 $mg \cdot kg^{-1}$ dose. AP; action potentials, BP; arterial blood pressure, Pt; tracheal pressure.

(RAR, n=7). Figure 1 shows a typical discharge pattern from both an SAR (A) and an RAR (B). Typically, the SARs maintained a steady rate of discharge while the tracheal pressure was above a threshold value. In contrast, the RARs showed a decreased firing frequency even as the tracheal pressure was increasing. The threshold values ranged from 4 to 20 cmH_2O for the fibers in this study. In the 10 units (8 SARs and 2 RARs) for which receptive fields were determined, their receptive fields were found to be distal to the main bronchus. The conduction velocities in SARs and RARs were between 16.4–35.4 $m \cdot sec^{-1}$ and 12.5–18.8 $m \cdot sec^{-1}$ respectively.

1) *responses of SARs to iv lidocaine*

Figure 2 shows an example of the effect of lidocaine 1 $mg \cdot kg^{-1}$ or 2 $mg \cdot kg^{-1}$ on a single SAR unit. The unit began to fire when the intratracheal pressure increased to about 5 cmH_2O. Following the injection of lidocaine, total suppression of the unit's activity developed rapidly within 10 seconds and was longer lasting following the 2 $mg \cdot kg^{-1}$ dose than after the 1 $mg \cdot kg^{-1}$ dose.

These effects of lidocaine on SARs were consistently observed and the duration of total suppression was less than 30 seconds and 15–50 seconds for the 1 $mg \cdot kg^{-1}$ and 2 $mg \cdot kg^{-1}$ dose respectively. Total suppression was followed by a period of imcomplete recovery. A lidocaine induced decrease in the total number of impulses resulting from each lung inflation recovered quickly to about 85% of the control within 2 min. Figure 3 (upper panel) shows effects of lidocaine (2 $mg \cdot kg^{-1}$) on the activity of a single SAR expressed as impulses per second.

These doses of lidocaine used in this study usually caused a dose-related decrease in blood pressure as shown in fig. 2. It was ascertained that a decrease in mean arterial pressure from 140 mmHg to 80 mmHg, induced by trimetaphan infusion, did not alter the phasic discharges of SARs evoked by pulmonary inflation. After lidocaine, increases in the intratracheal pressure, although less than 1 cmH_2O, were sometimes observed.

2) *responses of RARs to iv lidocaine*

Even a 2 $mg \cdot kg^{-1}$ dose of lidocaine did not produce an obvious suppression of RAR activity in any of the units studied. Because the firing pattern of RARs is irregular, it is difficult to say if there has been a change in a number of spikes per second following lidocaine (fig. 3).

3) *effects of iv lidocaine on efferent phrenic nerve activity*

Following iv lidocaine, total suppression of phrenic nerve activity developed within 10 sec. The duration of total suppression in the animal was significantly longer than the suppression of SAR activity (fig. 4). Spontaneous recovery of phrenic nerve activity was complete within 30 min. These results were obtained in all three cats in which it was studied. There was no significant change in $P_{ET}CO_2$ and P_T.

Discussion

It is well established that the discharge of SARs, activated by inflation of the lungs, exerts a primary function in the termination of inspiratory activity[9]. Few chemicals are known to excite SARs. RARs are greatly concentrated in the hilar airways and are shown to be the afferents responsible for the gasp reflex which is evoked by large rapid lung inflations[10]. Moreover, it is believed that the most important function of RARs is to signal the onset of pathophysiological changes in the airways, thus providing an efficient defense against various chemical and

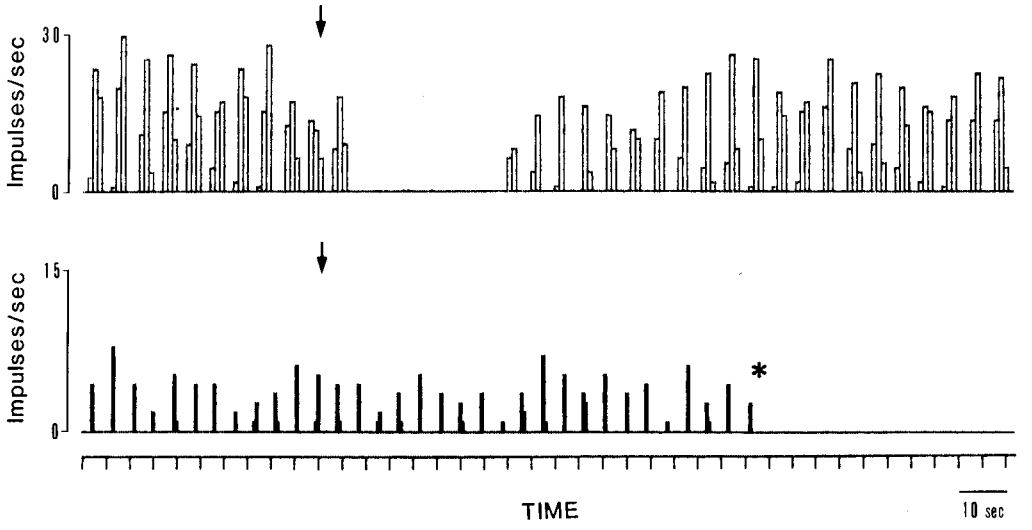

Fig. 3. Effects of lidocaine (2 mg·kg^{-1} iv) on an SAR and RAR are shown. At the arrows, lidocaine was injected. The x-axis represents time in seconds. The y-axis represents an absolute number of impulses per second. The upper panel is for an SAR and the lower panel for an RAR. Recording for an RAR was stopped at the mark *. Lidocaine produced a complete suppression of SAR activity. No obvious change in the number of RAR discharges was produced.

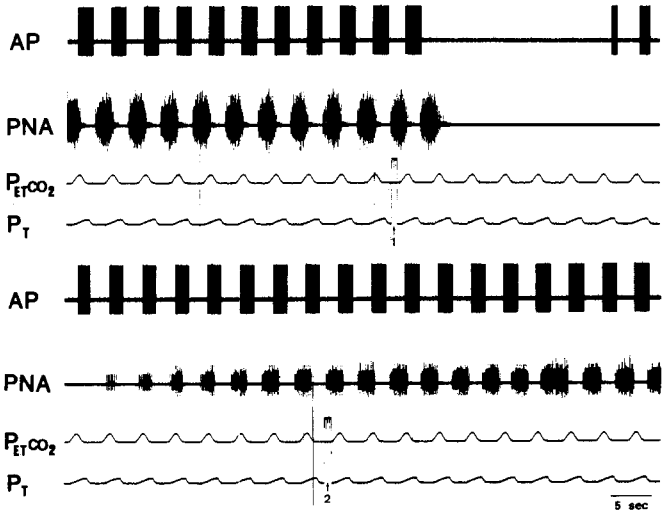

Fig. 4. Simultaneous recording of SAR activity and phrenic nerve activity. At the first bar mark (1), lidocaine (2 mg·kg^{-1}) was injected. Following the injection of lidocaine, both SAR activity and phrenic activity were completely suppressed within 10 seconds. Note, however, that phrenic nerve activity remained suppressed although not totally, whereas spontaneous recovery of SAR activity was complete within 1 min. The second bar mark (2) indicates the time "1 min after lidocaine". AP; action potentials of an SAR, PNA; phrenic nerve activity, $P_{ET}CO_2$; end-tidal concentration of CO_2, P_T; tracheal pressure.

mechanical irritants.

The results from this study show that iv lidocaine produces brief but complete suppression of SAR activity. Since actions in SARs are assumed to control inspiratory-to-expiratory switching, blocking their activity could be assumed to have an effect on prolonging inspiratory duration. However, iv lidocaine are shown to produce a respiratory arrest defined by abolition of phrenic nerve activity. In addition, we found that iv lidocaine did not produce a significant change in RAR activity. Considering the role of these afferent fibers (SARs and RARs)

in the airway, we could say that iv lidocaine mainly acts on CNS (respiratory center, vasomotor center and/or spinal motoneuron), resulting in cough suppression and prevention of hemodynamic changes.

We demonstrated that the phrenic nerve activity was completely suppressed following iv lidocaine (2 $mg \cdot kg^{-1}$). Our finding is in keeping with the fact[11] that iv lidocaine (1.5 $mg \cdot kg^{-1}$) suppresses cough evoked by citric acid inhalation in humans. Moreover, when comparing the effect of iv lidocaine on phrenic nerve activity with that on SAR activity in the same preparation, it is noticed that suppression of phrenic nerve activity was much longer than that of SAR activity. This finding support our hypothesis that the effect of iv lidocaine in the periphery on the SARs and RARs is not a direct mechanism responsible for the effects produced.

Intravenous lidocaine (1 or 2 $mg \cdot kg^{-1}$) suppress SAR activity totally but not RAR activity. It is not likely that the action of iv lidocaine on vagal afferent fibers play an important role in suppressing cough and in attenuating hemodynamic changes during airway stimulation.

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