Excitatory Mechanism of Deflationaly Slowly Adapting Pulmonary Stretch Receptors in the Rat Lung

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ABSTRACT

The excitatory responses of deflationaly slowly adapting pulmonary stretch receptor (SAR) activity to lung deflation ranging from approximately −15 to −25 cm of H2O for approximately 5 s were examined before and after administration of flecainide, a Na+ channel blocker, and K+ channel blockers, such as 4-aminopyridine (4-AP) and tetraethylammonium (TEA). The experiments were performed in anesthetized, artificially ventilated rats after unilateral vagotomy. The deflationaly SARs increased their activity during lung deflation and its effect became more pronounced by increasing the degree of negative pressure. During lung deflation the average values for the deflationaly SAR adaptation index (AI) were below 40%. Intravenous administration of veratridine (50 μg/kg), an Na+ channel opener, stimulated deflationaly SAR activity: one maintained excitatory activity mainly during deflation and the other receptors showed a tonic discharge during both deflation and inflation. Despite the difference in deflationaly SAR firing patterns after veratridine administration, flecainide treatment (6.0 mg/kg) blocked veratridine-induced deflationaly SAR stimulation and also caused strong inhibition of the excitatory responses of deflationaly SARs to lung deflation. Under these conditions, the average values for deflationaly SAR AI were over 90%. The responses of deflationaly SARs and deflationaly SAR AI to lung deflation were not significantly altered by pretreatment with either 4-AP (0.7 and 2.0 mg/kg) or TEA (2.0 and 6.0 mg/kg). These results suggest that the excitatory effect of lung deflation on deflationaly SAR activity is mediated by the activation of flecainide-sensitive Na+ channels on the nerve terminals of deflationaly SARs.

With the exception of rapidly adapting pulmonary stretch receptors and vagal C fibers, three different types of afferent receptors—inflationary pulmonary stretch, deflation-sensitiv, and irritant-like receptors—have been identified in the rat lung (Tsubone, 1986). Similar types of afferent units of the vagus nerve in the same species have been reported by Bergren and Peterson (1993); they suggested that three categories of receptors, as suggested by Tsubone (1986), belong to slowly adapting pulmonary stretch receptors (SARs). Based on the difference between phasic firing patterns of SARs in both closed and opened chest rats, Bergren and Peterson (1993) classified four subtypes of SARs: inflationary, most inflationary, deflationaly, and most deflationaly. Wei and Shen (1985) also demonstrated four different types of SARs in rabbits, cats, and monkeys (i.e., phasic and tonic inspiratory units and phasic and tonic expiratory units).

Although there may be differences in physiological function among the four different types of SARs, it has been proposed that the Hering-Breuer deflation reflex is mediated by the activation of deflationaly SARs (Knowlton and Larrabee, 1946; Tsubone, 1986). The deflationaly SARs are specific types of myelinated vagal afferent fibers responding to lung deflation on airway collapse. The thickening of the airway smooth muscle is considered to act as an effective stimulus for deflationaly SARs, which are oriented in a perpendicular manner to the axis of the smooth muscle (Bergren and Peterson, 1993). The mechanism mediating the mechanical deformation of deflationaly SARs has not yet been determined, but those receptors may have mechanosensitive channels on the endings. In the mechanoreceptor cells and spider mechanoreceptor neurons, ion channels responsible for the mechanically activated currents are mainly selective for Na+ rather than for K+ (Rydqvist and Purali, 1993; Juusola et al., 1994; Höger et al., 1997). In view of the action potential generation, both Na+ and K+ conductances have the ability to regulate the number of spikes with a cycle of Na+ inflow and K+ outflow, but the relationship between the activation of mechanosensitive channels on deflationaly SARs and the influx of Na+ or the efflux of K+ remains to be determined. On the other hand, the decrease in deflationaly SAR activity induced by lung collapse is slow, and the average values for deflationaly SAR adaptation index (AI) are 20%, indicating a slowly

ABBREVIATIONS: SARs, slowly adapting pulmonary stretch receptors; AI, adaptation index; Pτ, tracheal pressure; BP, blood pressure; MBP, mean BP; 4-AP, 4-aminopyridine; TEA, tetraethylammonium; Ia, fast-inactivating A-type current; I, sustained K+ current of delayed-rectifier type; TTX, tetrodotoxin.
adapting fashion (Tsubone, 1986). Bergren and Peterson (1993) found that the deflationary SAR AI was elevated above inflationary SARs at positive 20 cm of H$_2$O. From these observations, it is possible that the AI for deflationary SARs reflects faithfully the dynamic sensitivity of these receptors, which basically depends on the viscoelasticity of the structures containing deflationary SARs.

To investigate these relationships associated with lung deflation in an in vivo preparation, we performed different types of experiments in anesthetized artificially ventilated rats after unilateral vagotomy. First, the responses of deflationary SAR activity and deflationary SAR AI to deflation of the lungs were compared before and after administration of flecainide, one of the Na$^+$ channel blockers (Banitt et al., 1977; Campbell and Williams, 1983), sufficient to abolish veratridine-induced deflationary SAR stimulation. On the other hand, two broad classes of voltage-gated K$^+$ channel currents have been distinguished as to differences in time- and voltage-dependent properties: a typical fast-inactivating A-type current (I$_A$) and a more sustained K$^+$ current of delayed-rectifier type (I$_K$) (Storm, 1988; Halliwell, 1990). Two pharmacologically different types of K$^+$ channels are also identified in the myelinated axons of the rat sciatic nerve fibers: I$_A$ is blocked by 4-aminopyridine (4-AP) and I$_K$ is blocked by tetraethylammonium (TEA) (Baker et al., 1987; Kocsis et al., 1987). In other series of experiments, the changes in deflationary SAR activity and deflationary SAR AI in response to lung deflation were examined before and after administration of 4-AP or TEA. We selected deflationary SARs, as described in previous studies (Tsubone, 1986; Bergren and Peterson, 1993).

### Materials and Methods

**Animal Preparations.** The experiments were performed on 24 Wistar rats (300–380 g). They were anesthetized with sodium pentobarbital (45–50 mg/kg) given intraperitoneally. The trachea was exposed through a middle incision and cannulated below the larynx. The larynx and esophagus were retracted rostrally for nerve recording in a paraffin pool. Tracheal pressure (P$_T$) was measured by connecting a polyethylene catheter inserted into the tracheal tube to a pressure transducer. A polyethylene catheter was also inserted into the right jugular vein for administration of drugs or 0.9% NaCl solution. After administration of heparin (500 U/kg) into the jugular vein, the right common carotid artery was cannulated for measurement of blood pressure (BP). Then the left vagus nerve was exposed and sectioned, but the right vagus nerve was left intact. The animals were paralyzed with intravenous administration of gallamine (5–10 mg/kg), and additional doses (3–5 mg/kg) of gallamine were administered to avoid spontaneous respiratory movements, as required. The level of anesthesia, abolishing the changes in BP seen during the corneal reflex and pain reflexes induced by tail pinch, was maintained with additional doses of sodium pentobarbital (9–10 mg/kg/h) through a cannula inserted into the jugular vein. The stroke volume of the respirator was set at 10 ml/kg and its frequency ranged from 50 to 60 cycles/min.

**Experimental Procedures for Deflation and Inflation of the Lungs.** During artificial ventilation, the respirator was turned off at expiration. In that case, P$_T$ fell to 0 cm of H$_2$O. After occluding the inspiratory line of the respirator, the lungs were then subjected to negative pressure (approximately −15 to −25 cm of H$_2$O) for over 5 s. Subsequently, to reverse atelectasis, hyperinflation (inflation volume − 3 tidal volumes) was performed by means of a syringe connected to the expiratory line of the respirator. It took about 20 s to adjust the negative pressure to the next level before that pressure was applied to the lungs. The negative pressure was generated from the inlet port of a vacuum motor, changing the variable level, and connected to the expiratory line of the respirator. Concerning the inflation of the lungs, the respirator was initially turned off at expiration. Positive pressure (approximately +5 to +15 cm of H$_2$O) was then applied for over 5 s by increasing lung volume through a syringe connected to the expiratory line of the respirator.

**Measurement of Deflationary Slowly Adapting Pulmonary Stretch Receptors.** The peripheral end of the cut left vagus nerve was desheathed. Then a thin filament containing afferent nerve fibers was separated, placed on a unipolar silver electrode, and submerged in a pool of warm liquid paraffin (37–38°C). The small strands containing afferent nerve fibers were split until the single activity deflationary slowly adapting pulmonary stretch receptors (SARs) were identified, on the basis of their characteristic firing patterns during deflation as follows: 1) they fired during the deflation phase only; 2) the deflationary SAR discharge was inhibited by the inflation of the lungs; 3) the deflationary SARs discharge continued as long as the respirator was stopped; and 4) the increase in the receptor discharge occurred after forced deflation. We determined the AI of deflationary SARs on stopping the respirator in the deflation phase as well as during the deflation and inflation of the lungs as the peak frequency of the receptors during the experimental procedures minus the average frequency during the second of the procedures and then divided this by the peak frequency, by applying the method of Knowlton and Larrabee (1946) or Widdicombe (1954). This number was multiplied by 100 to obtain a percentage of adaptation. The value for AI of deflationary SARs was below 50%, as described by Tsubone (1986) and Bergren and Peterson (1993), particularly when lung deflation was maintained for over 5 s. The deflationary SAR activity was amplified with a preamplifier, and the individual receptor amplitude was selected with a window discriminator and fed into a counter. The number of impulses was recorded on a polygraph.

**Experimental Design.** Experiments were designed to test the roles of Na$^+$ and K$^+$ channels in the deflationary SAR responses to lung deflation. 1) In 12 deflationary SAR fibers in 12 rats, the effects of lung deflation for over 5 s on deflationary SAR activity, deflationary SAR AI, and P$_T$ were determined. Ten minutes after flecainide administration (6.0 mg/kg, i. v.) sufficient to abolish 50 μg/kg (i. v.) veratridine-induced deflationary SAR stimulation, the same sets of experiments were performed. The effectiveness of flecainide was determined by the absence of increased deflationary SAR activity after veratridine administration. 2) In six deflationary SAR fibers in six rats, the changes in deflationary SAR activity, deflationary AI and P$_T$ in response to lung deflation were examined. Ten minutes after intravenous administration of 4-AP (0.7 and 2.0 mg/kg), the same tests were repeated under the same conditions. The effectiveness of 4-AP effects was determined by the presence of increased deflationary SAR activity during lung deflation at 0 cm of H$_2$O. 3) In six deflationary SAR fibers in six rats, the effects of lung deflation on deflationary SAR activity, deflationary SAR AI, and P$_T$ were determined. Ten minutes after intravenous administration of TEA (2.0 and 6.0 mg/kg) the same sets of experiments were repeated. The absence of TEA effects was confirmed by restoring a slight decrease in either deflationary SAR activity or BP.

**Drugs.** Veratridine, 4-AP, and TEA were obtained from Sigma Chemical Co. (St. Louis, Mo), and flecainide was purchased from Eizai Pharmaceutical Co. Ltd. (Tokyo, Japan). Veratridine (10 mg) was dissolved in a small amount of weak HCl and diluted with 0.9% NaCl solution. Flecainide (10 mg) was dissolved in 5% glucose. 4-AP (10 mg) and TEA (10 mg) were dissolved in 0.9% NaCl solution.

**Statistical Analysis.** During control conditions, firing rates of the deflationary SARs during one whole respiratory cycle were measured over several respiratory cycles and expressed as impulses per second. The deflationary SAR responses to stopping the respirator for approximately 5 s, deflation (approximately −15 and −25 cm of H$_2$O) and inflation (approximately +5 and +15 cm of H$_2$O) of the
lungs for approximately 5 s, and veratridine administration (50 μg/kg) were obtained by counting the firing rates of receptors during the mechanical changes in the lungs and between onset of the increased receptor activity and recovery to the control level, and the average activities of deflationary SARs were calculated and expressed as impulses per second. Similarly, the control values for Pτ and mean BP (MBP) were averaged over several respiratory cycles and expressed as centimeters of H2O and mm Hg, respectively. The responses of Pτ and MBP to lung deflation and inflation and veratridine administration were obtained by measuring the respiratory parameters, as described above, and the average values for Pτ and MBP were expressed as centimeters of H2O and mm Hg, respectively. Under normal inflation, the statistical significance of the effects of veratridine (50 μg/kg), flecainide (6 mg/kg), and veratridine (50 μg/kg) plus flecainide (6 mg/kg) on the deflationary SAR activity was calculated by using a one-way analysis of variance for repeated measurements. The statistical significance of the effects of veratridine (6 mg/kg) on the responses of deflationary SAR activity, Pτ, and MBP to stopping the respirator, the deflation and inflation of the lungs, and veratridine administration was calculated by using a paired t test. For the deflationary SAR AI studies, values in the absence and presence of flecainide, 4-AP, or TEA were compared by using a paired t test. All values were expressed as mean ± S.E. A P value of less than 0.05 was considered statistically significant.

Results

The Firing Behavior of Deflationary SARs. Under control conditions, deflationary SARs discharged during deflation only (Fig. 1). Typical examples of the effects of stopping the respirator at the deflation phase, lung deflation, and lung inflation on deflationary SAR activity, Pτ, and BP are shown in Fig. 2. Stopping the respirator led to a train of impulses and caused an increase in the pulse pressure of BP (Fig. 2A). The deflation (approximately −25 cm of H2O) of the lungs stimulated deflationary SAR activity and the discharges continued in a slowly adapting fashion, and the response was associated with an increase in the pulse pressure of BP (Fig. 2B). In contrast, the activity of deflationary SARs was abolished by the inflation (approximately +15 cm of H2O) of the lungs, which reduced BP (Fig. 2C). In some deflationary SARs, lung inflation (approximately +15 cm of H2O) evoked a transient and burst activity, which adapted rapidly (Fig. 2D). The responses of deflationary SAR activity and deflationary SAR AI to the deflation and inflation of the lungs in 24 different deflationary SAR preparations in 24 rats are summarized in Fig. 3. The average discharges of deflationary SARs after stopping the respirator (0 cm of H2O) and during two different negative pressures (−14.6 ± 0.2 and −24.7 ± 0.3 cm of H2O) of lung deflation were 48.7 ± 3.7, 69.4 ± 3.9 and 101.3 ± 5.2 impulses per second, respectively, and the average values for deflationary SAR AI in those animals were 34.8 ± 2.6, 34.7 ± 2.5, and 34.7 ± 2.4%, respectively (Fig. 3A). Sixteen of 24 deflationary SARs showed silent activity during lung deflation ranging from approximately +5 to +15 cm of H2O. But the remaining eight deflationary SARs had very little activity during lung inflation, which usually showed a rapidly adapting fashion (Fig. 3B).

Effects of Flecainide on the Responses of Deflationary SARs to Veratridine and Lung Deflation. The administration of veratridine (50 μg/kg), a Na+ channel opener, caused excitation of the deflationary SAR activity during deflation, which was accompanied by a weak stimulation of the receptor activity in the inflation phase. Veratridine administration did not significantly alter the values for Pτ as an index of global bronchomotor tone (Fig. 4A). After administration of flecainide (6.0 mg/kg) in one of the Na+ channel blockers, the deflationary SARs decreased their activity in a 10-min period, and subsequent administration of veratridine (50 μg/kg) did not cause any excitation of the deflationary SAR activity (Fig. 4B). In 5 of 12 deflationary SARs, this type of the receptor was observed. As shown in Fig. 4C, veratridine (50 μg/kg) induced a tonic discharge of receptors during both inflation and deflation, and such firing patterns lasted for approximately 110 s, but the response was not associated with any significant change in Pτ. At 10 min after flecainide administration (6.0 mg/kg) this Na+ channel blocker abolished 50 μg/kg veratridine-induced deflationary SAR stimulation (Fig. 4D). Such an effect was seen in the seven remaining deflationary SARs. The effects of flecainide (6.0 mg/kg) on the deflationary SAR and Pτ responses to veratridine administration (50 μg/kg) during normal inflation (one tidal volume) is summarized in Fig. 5, A and B. During normal inflation, veratridine administration caused approximately a 1.6-fold increase in the deflationary SAR activity; this increase was abolished by pretreatment with flecainide, which reduced the baseline discharge of deflationary SARs (Fig. 5A). The changes in Pτ in response to normal ventilation were not altered by administration of either flecainide or veratridine (Fig. 5B).

Typical examples of the effects of flecainide (6.0 mg/kg) sufficient to block 50 μg/kg veratridine-induced deflationary
SAR stimulation on the responses of the receptor activity, $P_T$, and BP to lung deflation (approximately $-25$ cm of $H_2O$) are shown in Fig. 6, A and B. Pretreatment with flecainide greatly inhibited lung deflation-induced deflationary SAR stimulation, and the discharge pattern of the receptors changed from a slowly adapting fashion to a rapidly adapting one (Fig. 6, A and B). The effects of flecainide ($6.0$ mg/kg) to abolish veratridine-induced ($50 \mu g/kg$) deflationary SAR stimulation on the responses of the receptor activity and deflationary SAR AI to lung deflation of different pressures in 12 different deflationary SAR fibers in 12 rats are summarized in Fig. 6, C and D. The changes in $P_T$ produced by lung deflations were not significantly altered by pretreatment with flecainide. The $Na^+$ channel blocker flecainide significantly inhibited the excitatory responses of deflationary SAR activity to lung deflation with different pressures but caused a significant increase in the values for deflationary SAR AI. The MBP values during lung deflation at 0, $-14.7$ (average value), and $-24.6$ cm of $H_2O$ in the absence of flecainide were $108.6 \pm 5.3$, $112.7 \pm 5.9$, and $115.6 \pm 6.4$ mm Hg, respectively, and in the presence of flecainide, were $105.4 \pm 5.2$, $111.4 \pm 5.3$, and $114.6 \pm 6.2$ mm Hg, respectively. Although the maximal changes in MBP in response to lung deflations were not significantly altered by flecainide treatment, this $Na^+$ channel blocker caused bradycardia (lung deflation: absence, $-14.7$ cm of $H_2O$, $409.7 \pm 13.5$ beats/min; $-24.6$ cm of $H_2O$, $418.6 \pm 12.5$ beats/min; in the presence of flecainide at $6.0$ mg/kg, $-14.7$ cm of $H_2O$, $258.6 \pm 8.4$ beats/min, $n = 12, P < 0.05$; $-24.6$ cm of $H_2O$, $261.7 \pm 7.9$ beats/min, $n = 12, P < 0.05$).

**Effects of 4-AP on the Responses of Deflationary SARs to Lung Deflation.** Deflation (approximately $-25$ cm of $H_2O$) of the lungs stimulated deflationary SAR activity (Fig. 7A). After 10 min of 4-AP administration ($2.0$ mg/kg), the deflationary SARs increased their activity during deflation at 0 cm of $H_2O$, but the magnitude of the increased deflationary SAR activity during lung deflation was similar to that before 4-AP treatment (Fig. 7B). The change in $P_T$ in response to lung deflation before 4-AP treatment was the same as that after 4-AP treatment. The responses of defla-
Deflationary SARs and deflationary SAR AI to lung deflation with different pressures in six different deflationary SAR fibers in six rats were compared before and after 4-AP treatment (Fig. 7, C and D). The K⁺ channel blocker 4-AP at a dose of 2.0 mg/kg significantly increased the deflationary SAR activity seen after stopping the respirator, but this K⁺ channel blocker (0.7 and 2.0 mg/kg) did not significantly alter the excitatory effect of lung deflation on deflationary SAR activity. Furthermore, 4-AP treatment (0.7 and 2.0 mg/kg) had no significant effect on the values of deflationary SAR AI during lung deflation. The increase in BP occurred after administration of 4-AP, but this pressor effect was transient. The MBP values during lung deflation at 0, 14.8, and 24.7 cm of H₂O in the absence of 4-AP were 96.2 ± 4.8, 104.5 ± 5.3, and 108.2 ± 6.3 mm Hg, respectively, and in the presence of 4-AP (0.7 mg/kg), were 97.4 ± 4.9, 106.2 ± 5.4, and 110.4 ± 6.7 mm Hg, respectively, and 98.3 ± 4.9, 107.5 ± 5.7, and 112.5 ± 6.8 mm Hg, after 4-AP administration at 2.0 mg/kg, respectively. The maximal changes in MBP in response to lung deflations were not significantly altered by 4-AP treatment.

Effects of TEA on the Responses of Deflationary SARs to Lung Deflation. Figure 8, A and B, shows the

Deflationary SAR Stimulation and Na⁺ Channel

Fig. 4. Responses of deflationary SARs and P₁ to i.v. administration (▼) of veratridine (50 μg/kg) before (A and C) and after (B and D) administration of flecainide (6.0 mg/kg). Marked gaps (30 sec and 80 sec) indicate the elapsed time between recordings.

Fig. 5. Changes in deflationary SAR activity (A) and P₁ (B) in response to i.v. administration of veratridine (50 μg/kg) before and after pretreatment with flecainide (6.0 mg/kg) under normal inflation. □, control; ▲, veratridine (50 μg/kg); ●, flecainide (6.0 mg/kg); ○, veratridine (50 μg/kg) plus flecainide (6.0 mg/kg). Values are mean ± S.E.; n = 12. * P < 0.05, statistically significant difference from control values.

Fig. 6. Effects of flecainide on the responses of P₁ and deflationary SAR activity to lung deflation. A, control; B, after i.v. administration of flecainide (6.0 mg/kg); C, summary of the effects of lung deflation on deflationary SAR responses before (○) and after (●) flecainide treatment (6.0 mg/kg); D, summary of the effects of lung deflation on deflationary SAR AI responses before (○) and after (●) flecainide treatment (6.0 mg/kg). Values are mean ± S.E.; n = 12. * P < 0.05, statistically significant difference from control values.
responses of deflationary SAR activity and $P_T$ to deflation. $P_T$ to lung deflation. A, control; B, after i.v. administration of 4-AP (2.0 mg/kg); C, summary of the effects of lung deflation on deflationary SAR responses before (○) and after 4-AP treatment at 0.7 (▲) and 2.0 (◆) mg/kg; D, summary of the effects of lung deflation on deflationary SAR AI responses before (○) and after 4-AP treatment at 0.7 (▲) and 2.0 (◆) mg/kg. Values are mean ± S.E.; $n = 6$. * $P < 0.05$, statistically significant difference from control values.

Fig. 8. Effects of TEA on the responses of deflationary SAR activity and $P_T$ to lung deflation. A, control; B, after i.v. administration of TEA (6.0 mg/kg); C, summary of the effects of lung deflation on deflationary SAR responses before (○) and after TEA treatment at 2.0 (▲) and 6.0 (◆) mg/kg; D, summary of the effects of lung deflation on deflationary SAR AI responses before (○) and after TEA treatment at 2.0 (▲) and 6.0 (◆) mg/kg. Values are mean ± S.E.; $n = 6$.

Discussion

The present study provided evidence that excitation of the deflationary SAR activity during deflation of the lungs was greatly attenuated by pretreatment with an Na$^+$ channel blocker flecainide, whereas K$^+$ channel blockers, such as 4-AP and TEA, had no significant effect on the excitatory responses of deflationary SAR activity to lung deflation. Because the thickening of airway smooth muscle may be a possible stimulus of the receptor activity during lung deflation (Bergren and Peterson, 1993), it is conceivable that the mechanical deformation of deflationary SARs seen during lung deflation results in an increase in Na$^+$ influx via the activation of flecainide-sensitive (voltage-gated) Na$^+$ channels into the receptor endings, and as a result, this effect stimulates deflationary SAR activity.

Throughout collapse or forced deflation in the opened chest rat the discharges of deflationary SARs are known to show a slowly adapting fashion because during collapse the mean values for deflationary SAR AI were approximately 20% (Tsubone, 1986). Similar values for the AI of deflationary SARs in opened chest rats have been demonstrated by deflation to 0 cm of H$_2$O or by exposure to a constant-negative pressure of −10 cm of H$_2$O (Bergren and Peterson, 1993). In this study, all deflationary SARs fired during deflation only under normal ventilation, and they revealed persistent discharges consisting of train or burst impulses with normal ventilation and a train as well as a train followed by burst impulses with deflation of the lungs. During deflation to
treatment with flecainide (6.0 mg/kg) that blocked veratridine-induced deflationary SAR stimulation. This finding leads us to suggest that stimulation of deflationary SARs in the absence and presence of flecainide revealed firing patterns with a cardiac rhythm during normal ventilation as well as during deflation of lungs. Tsubone (1986) postulated that deflationary SARs are located in or near the hilus of the pulmonary artery or in a site in the lungs directly pulsed by the heartbeat. Further studies are needed to clarify the difference between the effects of deflationary and inflationary SARs on the transduction mechanism involving the functional coupling of Na\textsuperscript{+} channels and mechanosensitivities. In addition, after flecainide treatment, the AI of all deflationary SARs changed from a slowly adapting fashion to a rapidly adapting one. This probably implies that the activation of Na\textsuperscript{+} channels sensitive to the Na\textsuperscript{+} channel blocker flecainide contributes to the slowly adapting response of the deflationary SARs to the deflation of the lungs.

On the other hand, K\textsuperscript{+} conductances influence the shaping of action potentials, neuronal repetitive firing patterns, and the summation of synaptic inputs in neural cells (Mclarnon, 1995). Several different types of K\textsuperscript{+} channels have been identified on the basis of electrophysiological and pharmacological properties; the most widely distributed K\textsuperscript{+} currents are the Shaker (KV 1), Shaw (KV 2), Shal (KV 3), Shab (KV 4) (Butler et al., 1989; Wei et al., 1990), and a calcium-activated K\textsuperscript{+} channel current (I\textsubscript{CaK}) (Meech and Standen, 1975). Both I\textsubscript{Kp} (Shaker and Shal) and I\textsubscript{K} (Shab and Shaw) regulate the timing of action potential formation and the repetitive firing pattern of neuronal cells (Dekin and Getting, 1987; Spigelman et al., 1992). In the myelinated axons of the rat sciatic nerve fibers, 4-AP-sensitive K\textsuperscript{+} channels are related to action potential repolarization, but TEA-sensitive K\textsuperscript{+} channels cause posthyperpolarization after repetitive activity (Kocsis et al., 1987). The application of 4-AP is known to elicit a broad spike of action potentials (Kocsis et al., 1987; Poulter and Padjen, 1995), but such an effect could not be confirmed in this study because we measured extracellular action potentials. In this study, administration of 4-AP at a dose of 2.0 mg/kg increased deflationary SARs during lung deflation at 0 cm of H\textsubscript{2}O. This excitatory effect may be explained by evidence showing that 4-AP results in both membrane depolarization and repetitive firing in squids (Yeh et al., 1976, a,b). This was further supported by good evidence that 4-AP application (100 \mu M–1 mM) caused repetitive firing of action potentials in guinea pig airway sensory fibers (A\textdelta range) derived from cell bodies located within the nodose ganglion (McAlexander and Undem, 2000). But we found that prior treatment with TEA, inhibiting the I\textsubscript{K} conductance, had no significant effect on the activity of deflationary SARs under the deflation of the lungs at 0 cm of H\textsubscript{2}O. This finding is consistent with the observation that TEA (10 mM) application alone has little effect on the wave form of the compound action potentials obtained from the sciatic nerves of immature and mature rats but blocks 4-AP-induced postspike activity (hyperpolarization) (Eng et al., 1989). In addition, there is evidence that ganglion-derived airway sensory fibers (A\textdelta range) in the guinea pig are relatively insensitive to TEA application (10 mM) (McAlexander and Undem, 2000). It is therefore possible that TEA-sensitive K\textsuperscript{+} channels are not responsible for repolarization after sin-
gle action potentials. The fact that the AI values for deflationary SARs in the deflation of the lungs were not significantly altered by pretreatment with either 4-AP (0.7 and 2.0 mg/kg) or TEA (2.0 and 6.0 mg/kg) suggests that accommodation of the deflationary SAR discharge during the deflation of the lungs is not related to the activation of either I_h or I_K of the receptive terminal membranes. This was further confirmed by evidence that no detectable changes in deflationary SAR activity were found when different pressure deflations were applied to the lungs in the presence of 4-AP or TEA. From these results, it is more conceivable that the excitatory mechanism of deflationary SARs is not involved in the activation of either 4-AP sensitive or TEA-sensitive K⁺ channels.

The excitatory responses of deflationary SAR activity to the deflation of the lungs were greatly inhibited by pretreatment with flecainide, but pretreatment with 4-AP or TEA did not significantly alter those responses. The results suggest that stimulation of deflationary SARs by lung deflation is mainly mediated by the stimulating action of flecainide-sensitive (voltage-gated) Na⁺ currents on the receptor terminals of deflationary SARs.

References


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