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Inhibitory Mechanism of CO2 Inhalation on Slowly Adapting PHE JONES JOSEN DAN AND RECENTERAL THERAFEUTICS
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Pu **PUITTIONATY SITEICH RECEPIOTS IN INE ANESINEIIZED RADDII**
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ABSTRACT

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The inhibitory effects of CO₂ on slowly adapting pulmonary pretect receptors (SARs) were studied before and after admin-**ABSTRACT**
The inhibitory effects of CO₂ on slowly adapting pulmona
stretch receptors (SARs) were studied before and after admin-
istration of acetazolamide, a carbonic anhydrase inhibitor, **ABSTRACT**
The inhibitory effects of CO₂ on slowly adapting pulmonary pustretch receptors (SARs) were studied before and after admin-signtariation of acetazolamide, a carbonic anhydrase inhibitor, or kg
istration of acet **ABSTRACT**
The inhibitory effects of CO_2 on slowly adapting pulmonar
stretch receptors (SARs) were studied before and after admin
istration of acetazolamide, a carbonic anhydrase inhibitor, c
nifedipine, a calcium chann The inhibitory effects of CO_2 on slowly adapting pulmona
stretch receptors (SARs) were studied before and after admi
istration of acetazolamide, a carbonic anhydrase inhibitor,
nifedipine, a calcium channel blocker, in the immotory enects of CO_2 on slowly adapting painformary
stretch receptors (SARs) were studied before and after admin-
istration of acetazolamide, a carbonic anhydrase inhibitor, or kg).
nifedipine, a calcium channel b stretch receptors (SARS) were studied before and after admini-
istration of acetazolamide, a carbonic anhydrase inhibitor, or kg).
infedipine, a calcium channel blocker, in anesthetized, artifi-
cially ventilated rabbits a **dunned booker**, in anesthetized, artifi-

infedipine, a calcium channel blocker, in anesthetized, artifi-

cially ventilated rabbits after vagus nerve section. CO₂ inhala-

cortion (maximal tracheal CO₂ concentration rifedipline, a calculation channel blocket, in allest
inequiper cally ventilated rabbits after vagus nerve section. CO_2 inhala-
tion (maximal tracheal CO_2 concentration ranging from 7.2% to
deflation and deflation. Th tion (maximal tracheal CO_2 concentration ranging from 7.2% to
dete
9.5%) for approximately 60 sec decreased the receptor activity actic
during both inflation and deflation. The magnitude of decreased mon
receptor activi 9.5%) for approximately 60 sec decreased the receptor activity action was not found in the smooth muscle of either extrapul-
during both inflation and deflation. The magnitude of decreased monary or intrapulmonary bronchi

pulmonary stretch receptors to CO₂ inhalation, which were not
significantly influenced by pretreatment with nifedipine (1 mg/ pulmonary stretch receptors to CO_2 inhalation, which were not
significantly influenced by pretreatment with nifedipine (1 mg/
kg). Furthermore, CO_2 inhalation before and after vagal denerpulmonary stretch receptors to CO₂ inhalation, which were n
significantly influenced by pretreatment with nifedipine (1 m
kg). Furthermore, CO₂ inhalation before and after vagal dene
vation had no effect on total lung pulmonary stretch receptors to CO_2 inhalation, which were not
significantly influenced by pretreatment with nifedipine (1 mg/
kg). Furthermore, CO_2 inhalation before and after vagal dener-
vation had no effect on tota pulmonary stretch receptors to CO_2 inhalation, which were not
significantly influenced by pretreatment with nifedipine (1 mg/
kg). Furthermore, CO_2 inhalation before and after vagal dener-
vation had no effect on tota punificiantly influenced by pretreatment with nifedipine (1 mg/
kg). Furthermore, CO₂ inhalation before and after vagal dener-
vation had no effect on total lung resistance and dynamic lung
compliance. In another series Ag). Furthermore, CO_2 initiation before and after vagal defler-
vation had no effect on total lung resistance and dynamic lung
compliance. In another series of experiments, the staining to
determine the presence of carb validit had no effect off total lang resistance and dynamic lang
compliance. In another series of experiments, the staining to
determine the presence of carbonic anhydrase enzymatic re-
action was not found in the smooth m determine the presence of carbonic anhydrase enzymatic re-

Inhalation of CO₂ inhibits SARs in many species (Mustafa
and Purves, 1972; Schoener and Frankel, 1972; Inhalation of CO₂ inhibits SARs in many species (Mustafa
and Purves, 1972; Schoener and Frankel, 1972;
Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, Inhalation of CO₂ inhibits SARs in many species (Musta
and Purves, 1972; Schoener and Frankel, 197
Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogi
1976; Bradley *et al.*, 1976; Kunz *et al.*, 1976; Coleridge *et* Inhalation of CO₂ inhibits SARs in many species (Mustafa
and Purves, 1972; Schoener and Frankel, 1972;
Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio,
1976; Bradley *et al.*, 1976; Kunz *et al.*, 1976; Coleridg Inhalation of CO_2 inhibits SARs in many species (Mustafa hib and Purves, 1972; Schoener and Frankel, 1972; ada Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, itor 1976; Bradley *et al.*, 1976; Kunz *et al.*, and Purves, 1972; Schoener and Frankel, 1972; Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, 1976; Bradley *et al.*, 1976; Kunz *et al.*, 1976; Coleridge *et al.*, 1978), and the magnitude of the inhibitory effe 1976; Bradley *et al.*, 1976; Kunz *et al.*, 1976; Coleridge *et al.*, 1978), and the magnitude of the inhibitory effect depends on the location of the receptors (Mustafa and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Bar 1976; Bradley *et al.*, 1976; Kunz *et al.*, 1976; Coleridge *et al.*, b.
1978), and the magnitude of the inhibitory effect depends on the location of the receptors (Mustafa and Purves, 1972; (I
Sant'Ambrogio *et al.*, 19 1518), and the magnitude of the minimidal general depends on that
the location of the receptors (Mustafa and Purves, 1972; (Fit
Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, of S
1976). Furthermore, it can be Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, of S.
1976). Furthermore, it can be postulated that the variety of lula
this inhibition reflects different concentrations of CA in the San
smooth muscle of differe 1976). Furthermore, it can be postulated that the variety
this inhibition reflects different concentrations of CA in t
smooth muscle of different bronchi (Pack, 1981). However,
reports focus on the relationship between CO is inhibition reflects different concentrations of CA in the Sancooth muscle of different bronchi (Pack, 1981). However, no CO_2 ports focus on the relationship between CO_2 -induced SAR To hibition and CA activity in th

smooth muscle of different bronchi (Pack, 1981). However, no
reports focus on the relationship between CO_2 -induced SAR
inhibition and CA activity in the airway smooth muscle.
At present, two different mechanisms on CO_2 **reports focus on the relationship between** CO_2 **-induced SAR**
inhibition and CA activity in the airway smooth muscle.
At present, two different mechanisms on CO_2 -induced SAR
inhibition have been proposed: 1) The inhibit inhibition and CA activity in the airway smooth muscle.
At present, two different mechanisms on CO_2 -induced SA
inhibition have been proposed: 1) The inhibitory effect
mediated through changes in bronchial smooth muscle t At present, two different mechanisms on CO_2 -induced SAR
inhibition have been proposed: 1) The inhibitory effect is
mediated through changes in bronchial smooth muscle tone
divisestuem *et al.*, 1979; Mitchell *et al.*, inhibition have been proposed: 1) The inhibitory effect is
mediated through changes in bronchial smooth muscle tone
(Nilsestuem *et al.*, 1979; Mitchell *et al.*, 1980). 2) The inhib-
itory effect of CO_2 on SARs is inde mediated through changes in bronchial smooth muscle tone (Nilsestuem *et al.*, 1979; Mitchell *et al.*, 1980). 2) The inhibitory effect of CO_2 on SARs is independent of changes in lung mechanics (Mustafa and Purves, 1972 (Nilsestuem *et al.*, 1979; Mitchell *et al.*, 1980). 2) The inftitutive effect of CO_2 on SARs is independent of changes in lumechanics (Mustafa and Purves, 1972; Sant'Ambrogio *et* 1974; Coleridge *et al.*, 1978). Inde mechanics (Mustafa and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Coleridge *et al.*, 1978). Indeed, hypercapnic inhibition of SARs appears to be nonspecific and constitutes a generalized pH effect on neural function (Mus 1974; Coleridge *et al.*, 1978). Indeed, hypercapnic inhibition of SARs appears to be nonspecific and constitutes a generalized pH effect on neural function (Mustafa and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Bartlet 1974; Coleridge *et al.*, 1978). Indeed, hypercapnic inhibition tof SARs appears to be nonspecific and constitutes a generalized pH effect on neural function (Mustafa and Purves, 1972; is Sant'Ambrogio *et al.*, 1974; Bar and peaks to be honspective and constitutes a generalized pH effect on neural function (Mustafa and Purves, 1972; is
Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, g
1976; Coleridge *et al.*, 1978). For example The Ambrogio et al., 1974, Bartie
176; Coleridge *et al.*, 1978). For exametazolamide, a CA inhibitor, block
Received for publication January 29, 1996.

ABBREVIATIONS: SAR, slowly adapting pulmonary stretch receptor; CA, carbonic anhydrase; R_L, total lung resistance; Cdyn, dynamic lung **ABBREVIATIONS:** SAR, slowly adapting pulmonary stretch receptor; CA, carbonic anhy Sant'Ambrogio, 1976). In any event, the exact mechanism of
 CO_2 -induced SAR inhibition is still uncertain.

To elucidate whether there is a correlation between a specific

action of lung mechanics (airway smooth muscle CO_2 -induced SAR inhibition is still uncertain.
To elucidate whether there is a correlation between a specific
action of lung mechanics (airway smooth muscle tone) or a
nonspecific action of neural function and inhibitio To elucidate whether there is a correlation between a specification of lung mechanics (airway smooth muscle tone) or nonspecific action of neural function and inhibition of the SA activity associated with CO_2 inhalation, action of lung mechanics (airway smooth muscle tone) or a nonspecific action of neural function and inhibition of the SAR activity associated with CO_2 inhalation, we performed three different types of experiments in ane nonspecific action of neural function and inhibition of the SAR
activity associated with CO_2 inhalation, we performed three
different types of experiments in anesthetized, artificially ven-
tilated rabbits with or witho activity associated with CO_2 inhalation, we performed three different types of experiments in anesthetized, artificially ventilated rabbits with or without bilateral vagotomy. First, changes in R_L and Cdyn after CO_2 different types of experiments in anesthetized, artificially ventilated rabbits with or without bilateral vagotomy. First, changes in R_L and Cdyn after CO_2 inhalation were examined before and after vagus nerve section tilated rabbits with or without bilateral vagotomy. First changes in R_L and Cdyn after CO_2 inhalation were examine before and after vagus nerve section. Second, responses of SAI to inhalation of CO_2 gas mixtures wer changes in R_L and Cdyn after CO_2 inhalation were examined
before and after vagus nerve section. Second, responses of SARs
to inhalation of CO_2 gas mixtures were examined before and
after administration of acetazolam before and after vagus nerve section. Second, responses of SARs
to inhalation of CO_2 gas mixtures were examined before and
after administration of acetazolamide, a CA inhibitor, or nifed-
ipine, one of the L-subtype cal to inhalation of CO_2 gas mixtures were examined before and after administration of acetazolamide, a CA inhibitor, or nifed-
ipine, one of the L-subtype calcium blockers, in bilaterally vagotomized animals. In these stud after administration of acetazolamide, a CA inhibitor, or nife
ipine, one of the L-subtype calcium blockers, in bilaterally v
gotomized animals. In these studies, control values of trache
 CO_2 concentration were kept bel ipine, one of the L-subtype calcium blockers, in bilaterally vagotomized animals. In these studies, control values of tracheal CO_2 concentration were kept below 4%. The SARs have been classified into two different group $CO₂$ concentration were kept below 4%. The SARs have been classified into two different groups: "low-threshold" and "high-threshold" (Sant'Ambrogio, 1982; Ravi, 1986). The effects of acetazolamide and nifedipine on

hibition (Sant'Ambrogio *et al.*, 1974). In the case of slowly adapting mechanoreceptors of the cat's vibrissae, the inhibhibition (Sant'Ambrogio *et al.*, 1974). In the case of slow
adapting mechanoreceptors of the cat's vibrissae, the inhit
itory action of CO_2 was attributed to the release of protei hibition (Sant'Ambrogio *et al.*, 1974). In the case of sloved adapting mechanoreceptors of the cat's vibrissae, the infitory action of CO_2 was attributed to the release of prote bound calcium ions, because an increase hibition (Sant'Ambrogio *et al.*, 1974). In the case of sloved adapting mechanoreceptors of the cat's vibrissae, the inhitory action of CO_2 was attributed to the release of prote bound calcium ions, because an increase adapting mechanoreceptors of the cat's vibrissae, the inhibitory action of CO_2 was attributed to the release of protein-
bound calcium ions, because an increase in calcium concentration inhibited the discharge rate of t itory action of $CO₂$ was attributed to the release of proteinitory action of CO_2 was attributed to the release of proto bound calcium ions, because an increase in calcium conductration inhibited the discharge rate of those recept (Fitzgerald, 1940). It is possible that the inhibi bound calcium ions, because an increase in calcium concentration inhibited the discharge rate of those receptors (Fitzgerald, 1940). It is possible that the inhibitory response of SARs to CO_2 is mediated by ionic change Fitzgerald, 1940). It is possible that the inhibitory response
of SARs to CO_2 is mediated by ionic changes in the extracel-
lular fluid surrounding the sensory endings (Bartlett and
Sant'Ambrogio, 1976). In any event, t of SARs to CO_2 is mediated by ionic changes in the extracel-
lular fluid surrounding the sensory endings (Bartlett and
Sant'Ambrogio, 1976). In any event, the exact mechanism of
 CO_2 -induced SAR inhibition is still unc lular fluid surrounding the sensory endings (Bartlett and Sant'Ambrogio, 1976). In any event, the exact mechanism of CO_2 -induced SAR inhibition is still uncertain. To elucidate whether there is a correlation between a sp pulmonary stretch receptors to CO₂ inhalation, which were not
significantly influenced by pretreatment with infeddipine (1 mg/
kg). Furthermore, CO₂ inhalation before and after vagal dener-
vation had no effect on tot

threshold" (Sant'Ambrogio, 1982; Ranti-Ambrogio, 1982; Ranti-Ambrogi

1996
have been examined in two different groups of receptors. Third,
we evaluated the presence of CA enzymatic reaction within the **Pasame of the presence of CA enzymatic receptors. Third,**
we evaluated the presence of CA enzymatic reaction within the
smooth muscle of extrapulmonary and intrapulmonary bronchi. vs 1996
have been examined in two different groups of receptors. Third,
we evaluated the presence of CA enzymatic reaction within the
smooth muscle of extrapulmonary and intrapulmonary bronchi.
In additional experiments, we a have been examined in two different groups of receptors. Third, ca
we evaluated the presence of CA enzymatic reaction within the
smooth muscle of extrapulmonary and intrapulmonary bronchi.
In additional experiments, we als have been examined in two different groups of receptors. Third, cacodyl
we evaluated the presence of CA enzymatic reaction within the were examooth muscle of extrapulmonary and intrapulmonary bronchi. vacuum
In additional enzyme. **Experiments, we also determined we a specific or a nonspecific activity
Materials and Methods

we Thirty seven rebbits of both s**

Materials and Methods
Animal preparation. Thirty-seven rabbits of both sexes, weighwere administered as required. The trachea was exposed through a incubated in cobalt phosphate containing 10⁻⁶ M acetazolamide.
middle incision in the neck and cannulated below the larynx, and the **Experimental design.** trachea and esophagus were rostrally retracted to obtain space for ine the effect of CO_2 on lung mechanics, to test the role of a CA
paraffin pool. In 31 of the 37 rabbits, P_r was measured by connecting inhibitor in t trachea and esophagus were rostrally retracted to obtain space in
p. Additional doses (0.2–0.3 g/kg/hr, i.v.) of this anesthetic agent
were administered as required. The trachea was exposed through a
middle incision in th i.p. Additional doses (0.2–0.3 *g/kg/hr*, i.v.) of this anesthetic agent
were administered as required. The trachea was exposed through a
middle incision in the neck and cannulated below the larynx, and the
trachea and eso middle incision in the neck and cannulated below the larynx, and the trachea and esophagus were rostrally retracted to obtain space for in paraffin pool. In 31 of the 37 rabbits, P_T was measured by connecting in a polye a polyethylene catheter inserted into the tracheal tube to a differential pressure transducer in which one arm opened to the atmosphere.
After administration of heparin (500 U/kg) into the ear vein, the femoral artery was a polyethylene catheter inserted into the tracheal tube to a differential pressure transducer in which one arm opened to the atmosphere.
After administration of heparin (500 U/kg) into the ear vein, the femoral artery was tial pressure transducer in which one arm opened to the atmosphere. In After administration of heparin (500 U/kg) into the ear vein, the after administration of permediated for measurement of SAP. A polyeth-
ylene cathe After administration of heparin (500 U/kg) into the ear vein, the arfemoral artery was cannulated for measurement of SAP. A polyeth-
glene catheter was also inserted into the right external jugular vein, (k)
and its tip wa in a during the calibration of measurement of SER TH polycin

in and its tip was advanced into the right atrium for administration of

drugs or a 0.9% NaCl solution. The superior laryngeal and recurrent min

in advance. Th and its tip was advanced into the right atrium for administration of drugs or a 0.9% NaCl solution. The superior laryngeal and recurrent laryngeal nerves on both sides were identified, exposed and sectioned in advance. The drugs or a 0.9% NaCl solution. The superior laryngeal and recurrent maryngeal nerves on both sides were identified, exposed and sectioned min advance. Then the vagus nerves were exposed and sectioned. The 3) rectal tempera in advance. Then the vagus nerves were exposed and sectioned. The $3)$ lifered temperature was maintained at around 37° C by a heating pad. Fector and 34° C by a heating pad. The administration of gallamine trieth After the administration of gallamine trichlodide $(3-5 \text{ mg/kg}, i.v.)$ to inhanimals were artificially ventilated with air. The stroke volume of adminities respirator was set at 10 ml/kg, and its frequency ranged from 35 ments the respirator was set at 10 ml/kg, and its frequency ranged from 35 meto 45 cycles/min. Tracheal CO_2 concentration was measured by CO_2 gas analyzer (Respina IH 26, Sanei) and was kept at about 3.5% to pa 3.9% by adju

as analyzer (Respina IH 26, Sanei) and was kept at about 3.5% to
3.9% by adjusting the ventilatory rate.
Measurement of lung mechanics. In 7 of the 31 rabbits, \dot{V} was
measured by connecting the tracheal tube to a p 3.9% by adjusting the ventilatory rate.
 Measurement of lung mechanics. In 7 of the 31 rabbits, \dot{V} was measured by connecting the tracheal tube to a pneumotachograph and a differential pressure transducer, and the **Measurement of lung mechanics.** In 7 of the 31 rabbits, V was
measured by connecting the tracheal tube to a pneumotachograph so
and a differential pressure transducer, and the flow signal was
integrated to obtain V_T . P d a differential pressure transducer, and the flow signal was
egrated to obtain V_T . P_T was measured by using the technique
scribed previously. R_L and Cdyn were calculated by using the
nual graphic method reported by

integrated to obtain V_T . P_T was measured by using the technique weight of previously. R_L and Cdyn were calculated by using the was manual graphic method reported by Norlander *et al.* (1968). **Measurements of SAR ac** described previously. R_L and Cdyn were calculated by using the manual graphic method reported by Norlander *et al.* (1968). **Measurements of SAR activity.** The peripheral end of the cut left vagus nerve was desheathed. T manual graphic method reported by Norlander *et al.* (1968). and
 Measurements of SAR activity. The peripheral end of the cut

left vagus nerve was desheathed. To record single unit activity of

sARs, thin strands contai left vagus nerve was desheathed. To record single unit activity of to SARs, thin strands containing afferent nerve fibers were separated, coplaced on a unipolar silver electrode and submerged in a pool of moram liquid para SARs, thin strands containing afferent nerve fibers were separated, collected on a unipolar silver electrode and submerged in a pool of mean liquid paraffin (37°C-38°C). The SARs were identified, on the bybasis of their fi placed on a unipolar silver electrode and submerged in a pool of nearm liquid paraffin (37°C-38°C). The SARs were identified, on the basis of their firing behavior during lung inflation, as follows: 1) The fig. SARs increa warm nqua paramm (or σ so σ). The sinus were identified, on the basis of their firing behavior during lung inflation and decreased their discharge during deflation. 2) The increase in SAR activity was proportional to SARs increased their discharge during inflation and decreased their discharge during deflation. 2) The increase in SAR activity was The proportional to the increase in inflation volume of the respirator. 3) firin The disch The discharge of SARs continued as long as the tracheal tube was incoluded in a hyperinflated condition. The SAR activity was amplified and selected by a window discriminator for counting the number of impulses. It was als between the same increase and the solution. The SAR activity was amplified and selected by a window discriminator for counting the number confinition of the receptors obtained was determined and pulled rostrally. If the ca of impulses. It was also monitored on an oscilloscope and recorded on tivity), the time-dependent difference was compared between control
a polygraph. The location of the receptors obtained was determined and CO_2 -inhale a polygraph. The location of the receptors obtained was determined and by means of a balloon catheter. When the tip of the catheter reached use the carina, the balloon was inflated and pulled rostrally. If the The receptor by means of a balloon catheter. When the tip of the catheter reached
the carina, the balloon was inflated and pulled rostrally. If the
receptors were located below the carina, they were not stimulated by
pulling the inflat low-threshold receptors was influed and putch rootating. The receptors were located below the carina were confirmed in 24 rabbits. In these receptors, 14 were low-threshold receptors that fired during the whole respiratory carina were confirmed in 24 rabbits. In these receptors, 14 were low-threshold receptors that fired during the whole respiratory cycle, and the remainders were classified as high-threshold receptors that fired only during

puming the initiated bindom clutted: The 24 STRM focated Sciot are
carina were confirmed in 24 rabbits. In these receptors, 14 were
low-threshold receptors that fired during the whole respiratory cycle,
and the remainders Examination of an enzymatic reaction of CA in the airway
smooth muscle. In 6 of the 37 rabbits, under artificial ventilation
the chest was widely opened in the midline. A polyethylene catheter
was inserted into the left ve **EXAMIMATE CONSTROLUTE SOLUTE SET AND SET ALSO SET** the chest was widely opened in the midline. A polyethylene catheter
was inserted into the left ventricle, and its tip was advanced into the
ascending aorta. After the incision in the right appendage, a 0.9% the control we

Materials and Methods in the smooth muscle located in both extrapulmonary and intrapul-
monary bronchi in four rabbits. We also determined whether there
ing 3.0 to 3.5 kg, were anesthetized with urethane (1.0 g/kg) give **Pulmonary Stretch Receptor and CO₂ 403**
cacodylate buffer (0.05 M, pH = 7.4). The trachea and lung tissues
were excised immediately, and air from the lungs was sucked by a **Pulmonary Stretch Receptor and CO₂ 403** cacodylate buffer (0.05 M, pH = 7.4). The trachea and lung tissues were excised immediately, and air from the lungs was sucked by a vacuum pump. The trachea and lung tissues were **Pulmonary Stretch Receptor and CO₂ 403**
cacodylate buffer (0.05 M, pH = 7.4). The trachea and lung tissues
were excised immediately, and air from the lungs was sucked by a
vacuum pump. The trachea and lung tissues were cacodylate buffer $(0.05 \text{ M}, \text{pH} = 7.4)$. The trachea and lung tissues were excised immediately, and air from the lungs was sucked by a vacuum pump. The trachea and lung tissues were stored for 2 hr in the same fixative were excised immediately, and air from the lungs was sucked by a vacuum pump. The trachea and lung tissues were stored for 2 hr in the same fixative and then were immersed in a 20% sucrose solution, embedded in ornithi vacuum pump. The trachea and lung tissues were stored for 2 hr in the same fixative and then were immersed in a 20% sucrose solution, embedded in ornithine carbamoyl transferase compound and frozen. Frozen sections wit the same fixative and then were immersed in a 20% sucrose solution,
embedded in ornithine carbamoyl transferase compound and frozen.
Frozen sections with a thickness of 20 μ m were made on a cryostat
and reacted in Hans embedded in ornithine carbamoyl transferase compound and from
Frozen sections with a thickness of 20 μ m were made on a cryor
and reacted in Hansson's solution for 8 to 13 min (Hansson, 19
Sugai et al., 1981). Finally, Frozen sections with a thickness of 20 μ m were made on a cryostat
and reacted in Hansson's solution for 8 to 13 min (Hansson, 1967;
Sugai *et al.*, 1981). Finally, we examined an enzymatic reaction of CA
in the smooth ships and reduced in Finally, we examined an enzymatic reaction of CA in the smooth muscle located in both extrapulmonary and intrapulmonary bronchi in four rabbits. We also determined whether there was a specific reaction in the smooth muscle located in both extrapulmonary and intrapulmonary bronchi in four rabbits. We also determined whether there was a specific reaction of the CA enzyme in two rabbits. Frozen sections were initially incub monary bronchi in four rabbits. We also determined whether there
was a specific reaction of the CA enzyme in two rabbits. Frozen
sections were initially incubated according to the cobalt capture
method of Hansson (1967).

method of Hansson (1967). Afterwards, histological sections were
incubated in cobalt phosphate containing 10^{-5} M acetazolamide.
Experimental design. The experiments were designed to exam-
ine the effect of CO₂ on lu **Experimental design.** The experiments were designed to examine the effect of CO_2 on lung mechanics, to test the role of a CA inhibitor in the responses of SARs to CO_2 and to estimate any dependence of calcium influx inhibitor in the responses of SARs to CO_2 and to estimate any
dependence of calcium influx on CO_2 -induced SAR inhibition. The
following experiments were performed: 1) In seven rabbits, before
and after vagal denervati dependence of calcium influx on CO_2 -induced SAR inhibition. The following experiments were performed: 1) In seven rabbits, before and after vagal denervation, the effects of CO_2 inhalation for about 60 sec on P_T , R following experiments were performed: 1) In seven rabbits, before and after vagal denervation, the effects of CO_2 inhalation for about 60 sec on P_T , R_L and Cdyn were examined. 2) In 14 SAR fibers (low-threshold rece 60 sec on P_T , R_L and Cdyn were examined. 2) In 14 SAR fibers (low-threshold receptors = 5, high-threshold receptors = 5) in 14 rabbits, the effects of CO_2 inhalation on SAR activity were determined. Five minutes aft rabbits, the effects of CO_2 inhalation on SAR activity were determined. Five minutes after the administration of acetazolamide (20 mg/kg, i.v.), the same tests were repeated under the same conditions.
3) In 10 SAR fiber mined. Five minutes after the administration of acetazolamide (20 mg/kg, i.v.), the same tests were repeated under the same conditions.
3) In 10 SAR fibers (low-threshold receptors = 5, high-threshold receptors = 5) in 10

to inhalation of CO₂ gas mixtures were examined. Ten minutes after
administration of nifedipine (1 mg/kg, i.v.), the same sets of experi-
ments were repeated again.
Drugs. Acetazolamide (Takeda Pharmaceutical Cooperati ments were repeated again.
 Drugs. Acetazolamide (Takeda Pharmaceutical Cooperation, Japan, 500 mg) was diluted with 0.9% NaCl (20 mg/ml). Nifedipine (Sigma, USA, 10 mg) was dissolved in a small amount (1 ml) of ethanol **Drugs.** Acetazolamide (Takeda Pharmaceutical Cooperation, Japan, 500 mg) was diluted with 0.9% NaCl (20 mg/ml). Nifedipine (Sigma, USA, 10 mg) was dissolved in a small amount (1 ml) of ethanol and diluted with a 0.9% NaC Drugs. Accessoriance (Tancua Thankiece cooperation, expansion, 2018)
pan, 500 mg) was diluted with 0.9% NaCl (20 mg/ml). Nifedipine
(Sigma, USA, 10 mg) was dissolved in a small amount (1 ml) of
ethanol and diluted with a

ethanol and diluted with a 0.9% NaCl solution (1 mg/ml). The stock solution of nifedipine was kept in a bright protective glass container.
 Statistical analysis. During control conditions, V_T , \dot{V} and P_T were me solution of nifedipine was kept in a bright protective glass container.
 Statistical analysis. During control conditions, V_T , \dot{V} and P_T

were measured over several respiratory cycles, and R_L and Cdyn

were ca were measured over several respiratory cycles, and R_L and Cdyn
were calculated. The average values of P_T were expressed as cm H_2O ,
and the average values of R_L and Cdyn were expressed as cm H_2O /
Vsec and ml/cm and the average values of R_L and Cdyn were expressed as cm H_2O /
Vsec and m/cm H_2O , respectively. The responses of P_T , R_L and Cdyn
to CO_2 inhalation for approximately 60 sec (maximal tracheal CO_2
concentr l/sec and ml/cm H_2O , respectively. The responses of P_T , R_L and Cdyn
to CO_2 inhalation for approximately 60 sec (maximal tracheal CO_2
concentration ranging from 7.2% to 9.5%) were also calculated by
measuring al by the measurements of the measurements of $\frac{1}{2}$, $\frac{1}{2}$ and $\frac{1}{2}$ concentration ranging from 7.2% to 9.5%) were also calculated by measuring all three respiratory parameters at 10-sec intervals and by performi concentration ranging from 7.2% to 9.5%) were also calculated by
measuring all three respiratory parameters at 10-sec intervals and
by performing the measurements over 120 sec. Similarly, control
firing rates of the SARs measuring all three respiratory parameters at 10-sec intervals and
by performing the measurements over 120 sec. Similarly, control
firing rates of the SARs during both inflation and deflation were
averaged over several res by performing the measurements over 120 sec. Similarly, control
firing rates of the SARs during both inflation and deflation were
averaged over several respiratory cycles and expressed as imp/sec.
The SAR responses to CO₂ averaged over several respiratory cycles and expressed as imp/sec
The SAR responses to CO_2 inhalation were obtained by counting the
firing rates of receptors at 10-sec intervals and by performing the
measurements over 1 The SAR responses to CO_2 inhalation were obtained by counting the
firing rates of receptors at 10-sec intervals and by performing the
measurements over 120 sec, and the average activities of SARs
during both inflation a measurements over 120 sec, and the average activities of SARs
during both inflation and deflation were expressed as imp/sec. Con-
cerning the four measured parameters $(P_T, R_L, Cdyn)$ and SAR ac-
tivity), the time-dependent di during both inflation and deflation were expressed as imp/sec. Coverning the four measured parameters $(P_T, R_L, Cdyn$ and SAR ativity), the time-dependent difference was compared between contrand CO_2 -inhaled rabbits as well cerning the four measured parameters $(P_T, R_L, Cdyn$ and SAR activity), the time-dependent difference was compared between control and CO_2 -inhaled rabbits as well as before and after vagotomy by using a one-way analysis of and CO_2 -inhaled rabbits as well as before and after vagotomy by using a one-way analysis of variance for repeated measurements.
The effects of acetazolamide and nifedipine on the responses of SAR activities during infla using a one-way analysis of variance for repeated measurements.
The effects of acetazolamide and nifedipine on the responses of SAR
activities during inflation and deflation to CO_2 inhalation were also
analyzed by means activities during inflation and deflation to CO_2 inhalation were also analyzed by means of the modified *t* statistics. Then we used the Bonferroni test for one comparison $(k = 1)$ with the control. All values were expre analyzed by means of the modified t statistics. Then we used the

Results

Effect of CO₂ on lung mechanics. The values of P_T in e control were 9.1 ± 0.2 cm H_2O . Base-line R_L was 21.6 ± 1 **Results**
Effect of CO₂ on lung mechanics. The values of P_T in
the control were 9.1 \pm 0.2 cm H₂O. Base-line R_L was 21.6 \pm
2.9 cm H₂O/Vsec, and Cdyn was 2.7 \pm 0.3 mVcm H₂O. CO₂ **2.9 Effect of CO₂ on lung mechanics.** The values of P_T in the control were 9.1 ± 0.2 cm H_2O . Base-line R_L was 21.6 ± 2.9 cm H_2O .//sec, and Cdyn was 2.7 ± 0.3 m/cm H_2O . CO₂ inhalation for about 60 s **index Effect of CO₂ on lung mechanics.** The values of P_T in the control were 9.1 ± 0.2 cm H_2O . Base-line R_L was 21.6 ± 2.9 cm H_2O . Is and Cdyn was 2.7 ± 0.3 ml/cm H_2O . CO₂ inhalation for about 60 s

of increased tracheal $CO₂$ concentration. Values are means \pm S.E.; $n = 7$.

Fig. 2. Effect of acetazolamide on the responses of P_T , SARs (low-thre administration of acetazolamide (20 mg/kg). —, period of increased traches change in P_T , R_L or Cdyn in seven rabbits before and after vagal de **Fig. 2.** Effect of acetazolamide on the responses of P_T , SARs (low-threst administration of acetazolamide (20 mg/kg). —, period of increased tracheal change in P_T , R_L or Cdyn in seven rabbits before and after **F** v change in P_T , R_L or Cdyn in seven rabbits before and after
vagal denervation, which indicated that inhalation of CO_2 CO_2 inhalation. After CO_2 inhalation the SARs decreased
gas mixtures does not result in either

Example 1 and SAP to CO_2 inhalation. A) Control. B) After CO_2 concentration.
Effect of acetazolamide on the responses of SARs to O_2 **inhalation.** After CO_2 inhalation the SARs decreased reshold receptors) and SAP to CO_2 inhalation. A) Control. B) After eal CO_2 concentration.
 Effect of acetazolamide on the responses of SARs to CO_2 inhalation. After CO_2 inhalation the SARs decreased their activi eal CO₂ concentration.
 Effect of acetazolamide on the responses of SARs to
 CO_2 **inhalation.** After CO_2 inhalation the SARs decreased

their activity during both inflation and deflation. The de-

crease in the SA **Effect of acetazolamide on the responses of SARs to** CO_2 inhalation. After CO_2 inhalation the SARs decreased their activity during both inflation and deflation. The decrease in the SAR activity occurred approximately

1996
the onset of increased tracheal CO₂ concentration. The mag-
nitude of decreased SAR activity during deflation became 1996
the onset of increased tracheal CO_2 concentration. The magnitude of decreased SAR activity during deflation became
more prominent than that during inflation. The response was 1996
the onset of increased tracheal CO_2 concentration. The magnitude of decreased SAR activity during deflation became fl
more prominent than that during inflation. The response was
not associated with any significant the onset of increased tracheal CO_2 concentration. The magnetical of decreased SAR activity during deflation became flat more prominent than that during inflation. The response was tion not associated with any significa the onset of increased tracheal CO_2 concentration. The magnitude of decreased SAR activity during deflation became flucture prominent than that during inflation. The response was time to associated with any significant mitude of decreased SAR activity during deflation became
more prominent than that during inflation. The response was
not associated with any significant change in P_T . After CO_2
inhalation ceased, the SARs returned to not associated with any significant change in P_T . After CO_2 inhalation ceased, the SARs returned to their control activity within 30 sec (fig. 2A). The inhibitory effect of CO_2 inhalation inhalation ceased, the SARs returned to their control activity inhalation ceased, the SARs returned to their control activity
within 30 sec (fig. 2A). The inhibitory effect of CO_2 inhalation
on SAR activities was diminished by pretreatment with ac-
etazolamide (20 mg/kg), which eli within 30 sec (fig. 2A). The inhibitory effect of CO_2 inhalation
on SAR activities was diminished by pretreatment with ac-
etazolamide (20 mg/kg), which elicited severe hypocapnia
(tracheal CO_2 concentration $\lt 2\%$) etazolamide (20 mg/kg), which elicited severe hypocapnia (tracheal CO_2 concentration < 2%) and had no significant effect on SARs and P_T (fig. 2B). We compared the responses of nine different SARs (low-threshold recept (tracheal CO_2 concentration < 2%) and had no significant induced SAR inhibition reached a plateau at 10 sec after CO_2
effect on SARs and P_T (fig. 2B). We compared the responses inhalation, and the effect of CO_2 on (tracheal CO_2 concentration < 2%) and had no significan
effect on SARs and P_T (fig. 2B). We compared the response
of nine different SARs (low-threshold receptors) to CO_2 inhal
ation before and after pretreatment wit effect on SARs and P_T (fig. 2B). We compared the responses inhas of nine different SARs (low-threshold receptors) to CO_2 inha-
lation before and after pretreatment with acetazolamide (20 E mg/kg), a CA inhibitor (fi **2.2** to 55.0 ± 2.3 imp/sec, and the expiratory discharge of 2.2 to 55.0 ± 2.3 imp/sec, and the expiratory discharge of 2.2 ± 2.2 to 55.0 ± 2.3 imp/sec, and the expiratory discharge of inversion 62.2 ± 2.2 to 55.0 ± mg/kg), a CA inhibitor (fig. 3). At 10 sec after CO₂ inhalation, the inspiratory discharge of SARs was decreased from 62.2 \pm 2.2 to 55.0 \pm 2.3 imp/sec, and the expiratory discharge of receptors was decreased from

Pulmonary Stretch Receptor and CO₂ 405
sec. The decrease in SAR activities during inflation and de-
flation became more prominent at 40 sec after CO₂ inhala-**Pulmonary Stretch Receptor and CO₂ 40
sec. The decrease in SAR activities during inflation and d
flation became more prominent at 40 sec after CO₂ inhal
tion. The inhibitory effect of CO₂ inhalation on SAR activiti Pulmonary Stretch Receptor and CO₂ 405**
sec. The decrease in SAR activities during inflation and de-
flation became more prominent at 40 sec after CO_2 inhala-
tion. The inhibitory effect of CO_2 inhalation on SAR ac sec. The decrease in SAR activities during inflation and de-
flation became more prominent at 40 sec after CO_2 inhala-
tion. The inhibitory effect of CO_2 inhalation on SAR activities
during inflation and deflation was flation became more prominent at 40 sec after CO_2 inhalation. The inhibitory effect of CO_2 inhalation on SAR activities during inflation and deflation was significantly diminished by the treatment with acetazolamide. during inflation and deflation was significantly diminished
by the treatment with acetazolamide. The average dis-
charges of SARs (high-threshold receptors, $n = 5$) in control by the treatment with acetazolamide. The average disby the treatment with acetazolamide. The average discharges of SARs (high-threshold receptors, $n = 5$) in control
animals and acetazolamide (20 mg/kg)-treated animals were
64.7 \pm 2.4 and 62.1 \pm 2.3 imp/sec, respecti charges of SARs (high-threshold receptors, $n = 5$) in control
animals and acetazolamide (20 mg/kg)-treated animals were
64.7 \pm 2.4 and 62.1 \pm 2.3 imp/sec, respectively. The CO₂-
induced SAR inhibition reached a pl 64.7 \pm 2.4 and 62.1 \pm 2.3 imp/sec, respectively. The CO₂induced SAR inhibition reached a plateau at 10 sec after $CO₂$

inhalation. Administration of nifedipine (1 mg/kg) , a potent inhalation, and the effect of CO_2 on SARs was abolished by
pretreatment with acetazolamide (fig. 4).
Effect of nifedipine on the responses of SARs to CO_2
inhalation. Administration of nifedipine (1 mg/kg), a poten pretreatment with acetazolamide (fig. 4).
 Effect of nifedipine on the responses of SARs to CO₂ inhalation. Administration of nifedipine (1 mg/kg), a potent calcium channel blocker, had no significant effect on the in **Effect of nifedipine on the responses of SARs to C**
inhalation. Administration of nifedipine (1 mg/kg), a pote
calcium channel blocker, had no significant effect on t
inhibitory effect of CO_2 inhalation on low-thresh **inhalation.** Administration of nifedipine (1 mg/kg), a potent calcium channel blocker, had no significant effect on the inhibitory effect of CO_2 inhalation on low-threshold SARs ($n = 5$) (fig. 5). The CO_2 -induced SAR calcium channel blocker, had no significant e
inhibitory effect of CO_2 inhalation on low-thre
 $(n = 5)$ (fig. 5). The CO_2 -induced SAR (high-thre
tors, $n = 5$) inhibition was not significantly alt
treatment with nifedipi hibitory effect of CO_2 inhalation on low-threshold SARs = 5) (fig. 5). The CO_2 -induced SAR (high-threshold receptrs, $n = 5$) inhibition was not significantly altered by pre-
eatment with nifedipine at 1 mg/kg (fig. 6)

 $(n = 5)$ (fig. 5). The CO₂-induced SAR (high-threshold re
tors, $n = 5$) inhibition was not significantly altered by
treatment with nifedipine at 1 mg/kg (fig. 6).
Histochemical examination of CA activity in the
way sm tors, $n = 5$) inhibition was not significantly altered by pre-
treatment with nifedipine at 1 mg/kg (fig. 6).
Histochemical examination of CA activity in the air-
way smooth muscle. The smooth muscle in the extrapul-
 treatment with nifedipine at 1 mg/kg (fig. 6).
 Histochemical examination of CA activity in the air-
 way smooth muscle. The smooth muscle in the extrapul-

monary bronchi located below the carina did not exhibit any
 Histochemical examination of CA activity in the air-
way smooth muscle. The smooth muscle in the extrapul-
monary bronchi located below the carina did not exhibit any
CA activity (fig. 7A). CA activity was also not found **way smooth muscle.** The smooth muscle in the extrapulmonary bronchi located below the carina did not exhibit any CA activity (fig. 7A). CA activity was also not found in the smooth muscle of intrapulmonary bronchi, althou monary bronchi located below the carina did not exhibit any CA activity (fig. 7A). CA activity was also not found in the smooth muscle of intrapulmonary bronchi, although the alveolar epithelial cells exhibited CA activity veolar epithelial cells exhibited CA activity (fig. 7B). To determine whether the positive staining was due to a specific reaction of the CA enzyme, we stained adjacent sections in the absence and presence of acetazolamid veolar epithelial cells exhibited CA activity (fig. 7B). To determine whether the positive staining was due to a specific reaction of the CA enzyme, we stained adjacent sections in the absence and presence of acetazolamid termine whether the positive staining was due to a specific
reaction of the CA enzyme, we stained adjacent sections in
the absence and presence of acetazolamide $(10^{-5}$ M). As
shown in figure 8A-D, the staining of erthyr reaction of the CA enzyme, we stained adjacent sections in
the absence and presence of acetazolamide $(10^{-5}$ M). As
shown in figure 8A–D, the staining of erthyrocytes in the
blood vessels and of lung epithelial cells dis

Control 0 10 20 30 40 50 60 70 80 90 100 110 120

Time (sec)

Fig. 3. Changes in SAR activity (low-threshold receptors) in response to

CO₂ inhalation before (open circles) and after (closed circles) administion

CO₂ **CO2 CO2 CO2** Fig. 3. Changes in SAR activity (low-threshold receptors) in response to CO_2 inhalation before (open circles) and after (closed circles) administration of acetazolamide (20 mg/kg). 0, the onset of tracheal increased $CO_$ **Fig. 3.** Changes in SAR activity (low-tires CO₂ inhalation before (open circles) and tration of acetazolamide (20 mg/kg). 0, the CO₂ concentration. Values are means is ignificant difference from control values differ

to CO₂ inhalation before (open circles) and after (closed circles) administration of acetazolamide (20 mg/kg). 0, the onset of increased tracheal CO₂ concentration. Values are means \pm S.E.; $n = 5$. * P < .05 for Fig. 4. Changes in SAR activity (high-threshold receptors) in response
to CO_2 inhalation before (open circles) and after (closed circles) admin-
istration of acetazolamide (20 mg/kg). 0, the onset of increased tracheal

Control $\stackrel{1}{\text{O}}$ 10 $\stackrel{1}{\text{O}}$ 30 $\stackrel{1}{\text{O}}$ 50 60 $\stackrel{1}{\text{O}}$ 80 $\stackrel{1}{\text{O}}$ 10120 were

Fig. 5. Changes in SAR activity (low-threshold receptors) in response to

CO₂ inhalation before (open circles) and Fig. 5. Changes in SAR activity (low-threshold receptors) in response to CO₂ inhalation before (open circles) and after (closed circles) administration of nifedipine (1.0 mg/kg). 0, the onset of increased tracheal CO₂ **Fig. 5.** Changes in SAR activity (lo CO₂ inhalation before (open circle tration of nifedipine (1.0 mg/kg). 0
concentration. Values are means
difference from control values. conditions, the smooth muscle in both intrapulmonary and extrapulmonary bronching encoded interessed tracheal CO₂ obtoncentration. Values are means \pm S.E.; $n = 5$. $\pm P < .05$ for significant (M difference from control

concentration. Values are means \pm S.E.; $n = 5$. * P < .05 for significant (1)
difference from control values. (1)
conditions, the smooth muscle in both intrapulmonary and the
extrapulmonary bronchi did not show any spe difference from control values.

conditions, the smooth muscle in both intrapulmonary and

extrapulmonary bronchi did not show any specific reaction of

the CA enzyme.

Discussion

The inhibitory effects of CO_2 inhalation on SARs were freminished by acetazolamide, whereas nifedipine had no sig-
nificant effect on CO_2 -induced SAR inhibition. Because CA S. **Discussion** prepar

The inhibitory effects of CO₂ inhalation on SARs were from the

diminished by acetazolamide, whereas nifedipine had no sig-

nificant effect on CO₂-induced SAR inhibition. Because CA SARs a

activi **EXECUSSION**
The inhibitory effects of CO_2 inhalation on SARs wellminished by acetazolamide, whereas nifedipine had no
nificant effect on CO_2 -induced SAR inhibition. Because
activity was not found in the smooth muscle The inhibitory effects of CO_2 inhalation on SARs were
diminished by acetazolamide, whereas nifedipine had no sig-
nificant effect on CO_2 -induced SAR inhibition. Because CA
activity was not found in the smooth muscle o diminished by acetazolamide, whereas nifedipine had no sig-
nificant effect on CO_2 -induced SAR inhibition. Because CA SAI
activity was not found in the smooth muscle of the extrapul-
the
monary and intrapulmonary bronch mificant effect on CO_2 -induced SAR inhibition. Because CA SARs a
activity was not found in the smooth muscle of the extrapul-
monary and intrapulmonary bronchi, it is most likely that than b
inhibition of SAR activity b monary and intrapulmonary bronchi, it is most likely the inhibition of SAR activity by CO_2 does not involve changes ithe airway smooth muscle tone that depend upon the C activity. This is further confirmed by the fact t monary and intrapulmonary bronchi, it is most likel
inhibition of SAR activity by CO_2 does not involve chan
the airway smooth muscle tone that depend upon tl
activity. This is further confirmed by the fact that CO_2
la hibition of SAR activity by CO_2 does not involve changes in
e airway smooth muscle tone that depend upon the CA
tivity. This is further confirmed by the fact that CO_2 inha-
ition does not significantly alter either R

the airway smooth muscle tone that depend upon the CA low-
activity. This is further confirmed by the fact that CO_2 inha-
lation does not significantly alter either R_L or Cdyn.
The inhibitory effect of CO_2 on SARs i activity. This is further confirmed by the fact that CO_2 inha-
lation does not significantly alter either R_L or Cdyn.
The inhibitory effect of CO_2 on SARs is known to become due
more prominent under hypocapnic condi lation does not significantly alter either R_L or Cdyn.
The inhibitory effect of CO₂ on SARs is known to become
more prominent under hypocapnic conditions (Mustafa and
Purves, 1972; Sant'Ambrogio *et al.*, 1974; Bartlet more prominent under hypocapnic conditions (Mustafa and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Bartlett and Sant'Ambrogio, 1976; Bradley *et al.*, 1976). Thus tracheal CO_2 concentration was held below 4%, in the pre

Control 0 10 20 30 40 50 60 70 80 90 100 110 120

Time (sec)

Fig. 6. Changes in SAR activity (high-threshold receptors) in response

to CO₂ inhalation before (open circles) and after (closed circles) admini-

istration **Fig. 6.** Changes in SAR activity (high-thresh to CO_2 inhalation before (open circles) and a istration of nifedipine (1.0 mg/kg). 0, the o CO_2 concentration. Values are means \pm S significant difference from control istration of nifedipine (1.0 mg/kg). 0, the onset of increased tracheal CO_2 concentration. Values are means \pm S.E.; $n = 5$. * P < .05 for significant difference from control values.
iments, by adjusting the ventilato

CO₂ concentration. Values are means \pm S.E.; $n = 5$. *P < .05 for significant difference from control values.
iments, by adjusting the ventilatory rate and/or the inflation volume of the respirator. The SARs recorded significant difference from control values.

iments, by adjusting the ventilatory rate and/or the inflation

volume of the respirator. The SARs recorded in this study

were similar to those of the receptors obtained in pr iments, by adjusting the ventilatory rate and/or the inflation
volume of the respirator. The SARs recorded in this study
were similar to those of the receptors obtained in previous
studies (Matsumoto *et al.*, 1990; 1993). studies, by adjusting the ventriation y rate and/or the initiation
volume of the respirator. The SARs recorded in this study
were similar to those of the receptors obtained in previous
studies (Matsumoto *et al.*, 1990; 1 volume of the respirator. The SARs recorded in this study were similar to those of the receptors obtained in previous studies (Matsumoto *et al.*, 1990; 1993). Thus the SARs in this study may belong to the same category of were similar to those of the receptors obtained in previous
studies (Matsumoto *et al.*, 1990; 1993). Thus the SARs in this
study may belong to the same category of type II receptors as
obtained in the SAR responses to sta studies (Matsumoto *et al.*, 1990; 1993). Thus the SARs in this study may belong to the same category of type II receptors as obtained in the SAR responses to static pressure inflations (Miserocchi and Sant'Ambrogio, 1974 study may belong to the same category of type II receptors as
obtained in the SAR responses to static pressure inflations
(Miserocchi and Sant'Ambrogio, 1974). Sant'Ambrogio *et al.*
(1974) demonstrated that the inhibitory obtained in the SAR responses to static pressure inflation (Miserocchi and Sant'Ambrogio, 1974). Sant'Ambrogio *et a* (1974) demonstrated that the inhibitory action of inhale CO_2 on bronchial SARs appeared faster than t (Miserocchi and Sant'Ambrogio, 1974). Sant'Ambrogio *et* (1974) demonstrated that the inhibitory action of inhal CO_2 on bronchial SARs appeared faster than that on ϵ trapulmonary SARs. Furthermore, in an earlier st (1974) demonstrated that the inhibitory action of inhaled CO_2 on bronchial SARs appeared faster than that on ex-
trapulmonary SARs. Furthermore, in an earlier study, Brad-
ley *et al.* (1976) reported that CO_2 inhalat CO_2 on bronchial SARs appeared faster than that on ex-
trapulmonary SARs. Furthermore, in an earlier study, Brad-
ley *et al.* (1976) reported that CO_2 inhalation did not signif-
icantly influence the activity of trac trapulmonary SARs. Furthermore, in an earlier study, Brad-
ley *et al.* (1976) reported that CO_2 inhalation did not signif-
icantly influence the activity of tracheal SARs. We therefore
decided to investigate the inhibi ley *et al.* (1976) reported that CO_2 inhalation did not significantly influence the activity of tracheal SARs. We therefore decided to investigate the inhibitory effect of CO_2 in our SAR preparations. Moreover, CO_2 decided to investigate the inhibitory effect of CO_2 in our SAR
preparations. Moreover, CO_2 -induced SAR inhibition is ob-
served even when the change in the airway CO_2 is isolated
from that in the blood CO_2 (Sant'A decided to investigate the inhibitory effect of CO_2 in our SAR
preparations. Moreover, CO_2 -induced SAR inhibition is ob-
served even when the change in the airway CO_2 is isolated
from that in the blood CO_2 (Sant'A preparations. Interver, CO_2 -induced SAR inhibition is observed even when the change in the airway CO_2 is isolated from that in the blood CO_2 (Sant'Ambrogio *et al.*, 1974; Bradley *et al.*, 1976; Coleridge *et al.*, from that in the blood CO_2 (Sant'Ambrogio *et al.*, ley *et al.*, 1976; Coleridge *et al.*, 1978). The rapis SARs after CO_2 inhalation in this study may be the change in the bronchial lumen CO_2 concentration. Then b y et al., 1976; Coleridge et al., 1978). The rapid reaction of ARs after CO_2 inhalation in this study may be explained by e change in the bronchial lumen CO_2 concentration rather an by variation in the blood CO_2 co the change in the bronchial lumen CO_2 concentration rather
than by variation in the blood CO_2 concentration.
During CO_2 inhalation, the SARs that were classified as

SARs after CO_2 inhalation in this study may be explained by
the change in the bronchial lumen CO_2 concentration rather
than by variation in the blood CO_2 concentration.
During CO_2 inhalation, the SARs that were cl During CO_2 inhalation, the SARs that were classified as
low-threshold receptors decreased their activity during both
inflation and deflation. The magnitude of decreased SAR
activity during deflation became more pronounc low-threshold receptors decreased their activity during both inflation and deflation. The magnitude of decreased SAR activity during deflation became more pronounced than that during inflation. These results are in agreeme low-threshold receptors decreased their activity during both
inflation and deflation. The magnitude of decreased SAR
activity during deflation became more pronounced than that
during inflation. These results are in agreeme activity during deflation became more pronounced than that
during inflation. These results are in agreement with obser-
vations indicating a greater inhibition of SAR activity during
deflation (Mustafa and Purves, 1972; Sa activity during deflation became more pronounced than th
during inflation. These results are in agreement with obs
vations indicating a greater inhibition of SAR activity duri
deflation (Mustafa and Purves, 1972; Sant'Ambr during inflation. These results are in agreement with observations indicating a greater inhibition of SAR activity during deflation (Mustafa and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Bradley *et al.*, 1976; Coleridg

Fig. 7. A) Light micrograph of the extrapulmonary airways for CA enactivity. B) Light micrograph of the intrapulmonary airways for CA enactivity. Lung epithelial cells (arrow) show intense staining, but smooth the muscles Fig. 7. A) Light micrograph of the extrapulmonary airways for CA
activity. B) Light micrograph of the intrapulmonary airways for CA
activity. Lung epithelial cells (arrow) show intense staining, but smooth
muscles (star) d

muscles (star) do not show staining (\times 100). C) C-shaped tracheal
cartilage. E) Epithelium of trachea.
to the difference in transmural pressure between inflation
and deflation. This interpretation is further supported b cartilage. E) Epithelium of trachea.
to the difference in transmural pressure between inflation
and deflation. This interpretation is further supported by
evidence that the inhibitory effect of CO_2 on SARs is weaker
at to the difference in transmural pressure between inflation
and deflation. This interpretation is further supported by
evidence that the inhibitory effect of CO_2 on SARs is weaker
at the higher transmural pressures (Must and deflation. This interpretation is further supported
and deflation. This interpretation is further supported
evidence that the inhibitory effect of CO₂ on SARs is wea
at the higher transmural pressures (Mustafa and Pu and denation. This interpretation is further supported b
evidence that the inhibitory effect of CO_2 on SARs is weake
at the higher transmural pressures (Mustafa and Purve
1972; Bradley *et al.*, 1976). In addition, duri at the higher transmural pressures (Mustafa and Purves, 1972; Bradley *et al.*, 1976). In addition, during CO_2 inhalation the peak inspiratory discharge of SARs in both high-threshold and low-threshold receptors decreas at the inglier transmitted pressures (mustaid and 1 dives, the
1972; Bradley *et al.*, 1976). In addition, during CO_2 inhala-
tion the peak inspiratory discharge of SARs in both high-
threshold and low-threshold recepto tion the peak inspiratory discharge of SARs in both high-
threshold and low-threshold receptors decreased. The de-
crease in high- and low-threshold SAR responses to CO_2 pressure that passes through the nerve endings of receptors
threshold and low-threshold receptors decreased. The de-
crease in high- and low-threshold SAR responses to CO_2
inhalation could be explained by reduction of t $\frac{d}{dt}$
 $\frac{d}{dt}$
 $\frac{d}{dt}$ in high-
 $\frac{d}{dt}$ inflation
 $\frac{d}{dt}$ The $\frac{d}{dt}$ CO₂-indu France III in the CO₂-induced SAR inhibition is mediated by augments of the transmit essure that passes through the nerve endings of recepting inflation.
The CO₂-induced SAR inhibition is mediated by augmetion of bronc

Imialation collube explained by reduction of the transmittar
pressure that passes through the nerve endings of receptors
during inflation.
The CO₂-induced SAR inhibition is mediated by augmen-
tation of bronchial smooth b

The CO₂-induced SAR inhibition is mediated by augmentation of bronchial smooth muscle tone (Nilsestuem *et al.*, h

1979; Mitchell *et al.*, 1980). Conversely, inhibition of SARs by in

CO₂ is independent of changes Ine CO₂-induced SAR inhibition is mediated by augmentation of bronchial smooth muscle tone (Nilsestuem *et al.*, 1979; Mitchell *et al.*, 1980). Conversely, inhibition of SARs by CO₂ is independent of changes in lung m 1979, Michell et al., 1980). Conversely, immotion of SARS by
CO₂ is independent of changes in lung mechanics (Mustafa
and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Coleridge *et al.*,
1978). Studies in the presence of co. $\frac{1}{2}$ is independent of changes in lang mechanics (must
and Purves, 1972; Sant'Ambrogio *et al.*, 1974; Coleridge *et a*
1978). Studies in the presence of intact vagal efferent inne
vation to the airways have demo **1978).** Studies in the presence of intact vagal efferent inner-
1978). Studies in the presence of intact vagal efferent inner-
vation to the airways have demonstrated that hypercapnia in
causes a cholinergic-mediated i is 1918). Statutes in the presence of intact vagar enerent inner-
vation to the airways have demonstrated that hypercapnia ing
causes a cholinergic-mediated increase in R_L (Widdicombe, dete
1966; Martin *et al.*, 1995). This finding implies that the increase in R_L (what controller).

1966; Martin *et al.*, 1995). In this study, we found that CO_2 and $Cdyn$ in rabbits before and after vagus nerve section.

This finding implies that the inhalation had no significant effect on lung mechanics $(R_L$ and Cdyn) in rabbits before and after vagus nerve section.
This finding implies that the increase of bronchomotor tone induced by CO_2 is attenuated by reflex a

Pulmonary Stretch Receptor and CO₂ 407
and Widdicombe, 1962) and/or by stimulation of sympathetic
outflow to the airways. Therefore, it is reasonable to assume **Pulmonary Stretch Receptor and CO₂ 407**
and Widdicombe, 1962) and/or by stimulation of sympathetic
outflow to the airways. Therefore, it is reasonable to assume
that the mechanism by which CO₂ inhibits SARs is not reand Widdicombe, 1962) and/or by stimulation of sympathetic outflow to the airways. Therefore, it is reasonable to assume that the mechanism by which CO_2 inhibits SARs is not related to changes in bronchial smooth muscle outflow to the airways. Therefore, it is reasonable to assume
that the mechanism by which CO_2 inhibits SARs is not re-
lated to changes in bronchial smooth muscle tone. On the
other hand, there is evidence that the sens lated to changes in bronchial smooth muscle tone. On the other hand, there is evidence that the sensitivity of SARs to CO_2 depends on their location in the tracheobronchial tree (Sant'Ambrogio *et al.*, 1974; Bradley *e* other hand, there is evidence that the sensitivity of SARs to CO_2 depends on their location in the tracheobronchial tree (Sant'Ambrogio *et al.*, 1974; Bradley *et al.*, 1976). According to Pack (1981), who suggested th to Pack (1981), who suggested that the differences in sensitivity may be related the different concentrations of CA activity in the walls of different bronchi. However, there are no studies to confirm this suggestion. In t **example is also different concentrations of CA activity in the walls of different bronchi. However, there are no**
studies to confirm this suggestion. In this study, the positive
staining of the erythrocytes in blood vesse enzyme in the wants of unterent bronch. Trowever, there are no
studies to confirm this suggestion. In this study, the positive
staining of the erythrocytes in blood vessels and the alveolar
epithelial cells was based on a staining of the erythrocytes in blood vessels and the alveolar
epithelial cells was based on a specific reaction of the CA
enzyme. Because there was no significant staining for CA
enzymatic reaction in the smooth muscle of epithelial cells was based on a specific reaction of the CA enzyme. Because there was no significant staining for CA enzymatic reaction in the smooth muscle of extrapulmonary and intrapulmonary bronchi, we concluded that epithelial cens was based on a specific reaction of the CA
enzyme. Because there was no significant staining for CA
enzymatic reaction in the smooth muscle of extrapulmonary
smoth muscle.
SAR inhibition is not related to enzymatic reaction in the smooth muscle of extrapulmonary
and intrapulmonary bronchi, we concluded that CO_2 -induced
SAR inhibition is not related to the CA activity in the airway
smooth muscle.
Sant'Ambrogio *et al.* (19

activity. B) Light micrograph of the intrapulmonary airways for CA Riley *et al.*, 1988; Szaboks *et al.*, 1989), similar localization of activity. Lung epithelial cells (arrow) show intense staining, but smooth muscles (SAR inhibition is not related to the CA activity in the airway
smooth muscle.
Sant'Ambrogio *et al.* (1974) reported that administration of
acetazolamide (35 mg/kg) blocked the inhibitory effects of
CO₂ on the discharge **CO2** on the discharge of SARs in dogs. However, they did not examine whether the effect of accetazolamide (35 mg/kg) blocked the inhibitory effects of CO_2 on the discharge of SARs in dogs. However, they did not examine Sant'Ambrogio *et al.* (1974) reported that administration of acetazolamide (35 mg/kg) blocked the inhibitory effects of CO_2 on the discharge of SARs in dogs. However, they did not examine whether the effect of acetazol acetazolaline (35 ingles) blocked the filmbitory effects of
CO₂ on the discharge of SARs in dogs. However, they did not
examine whether the effect of acetazolamide at a higher dose
is due to a specific action of the drug examine whether the effect of acetazolamide at a higher dose
is due to a specific action of the drug. We showed that the
inhibitory effect of CO_2 inhalation for approximately 60 sec
on SARs (low-threshold and high-thres is due to a specific action of the drug. We showed that the inhibitory effect of CO_2 inhalation for approximately 60 sec on SARs (low-threshold and high-threshold receptors) was reduced by the administration of acetazol is ute to a specific action of the urig. We showed that the
inhibitory effect of CO₂ inhalation for approximately 60 secon SARs (low-threshold and high-threshold receptors) was
reduced by the administration of acetazolam minionary enect of CO_2 inhibitant of approximately obset
on SARs (low-threshold and high-threshold receptors) was
reduced by the administration of acetazolamide, a CA inhib-
itor, at 20 mg/kg. Maren (1977) demonstrated on SARs (low-threshold and high-threshold receptors) was
reduced by the administration of acetazolamide, a CA inhib-
itor, at 20 mg/kg. Maren (1977) demonstrated that the dos-
ages of acetazolamide of 20 mg/kg or less inh From the CA enzyme in the lung, except for the smooth muscle.
Because of acetazolamide of 20 mg/kg or less inhibit 99.99% of
the enzyme and do not have any nonspecific effect. Thus
CO₂-induced SAR inhibition is closely ages of actiazoraline of 20 mg/kg of ress minior 93.93% of
the enzyme and do not have any nonspecific effect. Thus
 CO_2 -induced SAR inhibition is closely related to the presence
of the CA enzyme in the lung, except fo CO₂-induced SAR inhibition is closely related to the presence
of the CA enzyme in the lung, except for the smooth muscle.
Because CA activity has been identified in myelinated affer-
ent fibers in peripheral nerves (Camm Because CA activity has been identified in myelinated afferent fibers in peripheral nerves (Cammaer and Transey, 1987; ent nerves in the airways have not been reported.

pressure that passes through the nerve endings of receptors intracellular Cl^- levels cause hyperpolarization of the mem-
during inflation.
The CO_2 -induced SAR inhibition is mediated by augmen-
tation of bronchial smoot **We believe the proposed model shown in figure 9 explains** exchange systems. The cell membranes are known to be Frowever, studies to investigate the CA localization of a
flerious inter-
ent nerves in the airways have not been reported.
We believe the proposed model shown in figure 9 explains
Cl⁻ transport involving both Cl⁻ \leftrightarrow Free to CO₂ but relatively impermeable to CO₂ but relatively impermeable to CO_2 but relatively impermeable to HO_3^- . The intracellular CO_2 is hydrated to HO_3^- + H⁺ and is greatly accelerated by the intracellu Cl⁻ transport involving both Cl⁻ \leftrightarrow Cl⁻ and Cl \leftrightarrow HCO₃ exchange systems. The cell membranes are known to be freely permeable to CO_2 but relatively impermeable to HCO_3^- . The intracellular CO_2 is hydrated be a tendency for HCO₂ but relatively impermeable to HCO_3^- . The intracellular CO_2 is hydrated to HCO_3^- + H^+ and is greatly accelerated by the intracellular CA. Thus there will be a tendency for HCO_3^- to excha the magnitude of increased by the intracellular CA. Thus there will
be a tendency for HCO_3^- to exchange with external Cl via
 $HCO_3^- \leftrightarrow Cl^-$ exchange carrier, and this process depends on
the magnitude of increased CO_2 lev is greatly accelerated by the intracellular CA. Thus there we
be a tendency for HCO_3^- to exchange with external Cl v
 $HCO_3^- \leftrightarrow Cl^-$ exchange carrier, and this process depends of
the magnitude of increased CO_2 levels. Hen $HCO₃⁻ \leftrightarrow Cl⁻$ exchange carrier, and this process depends on the magnitude of increased $CO₂$ levels. Hence the increased the magnitude of increased CO_2 levels. Hence the increased
intracellular Cl⁻ levels cause hyperpolarization of the mem-
brane potential of the SAR terminal and elevate the thresh-
old of action potential generation, r old of action potential generation, resulting in a greater in-
hibition of the expiratory discharge of SARs during CO_2
inhibition. Therefore, it is more plausible that blockade of
 CO_2 hydration after the administratio old of action potential generation, resulting in a greater in-
hibition of the expiratory discharge of SARs during CO_2
inhibition. Therefore, it is more plausible that blockade of
 CO_2 hydration after the administratio mbition. Therefore, it is more plausible that blockade $CO₂$ hydration after the administration of a CA inhibitor α to depolarize hyperpolarization of the membrane potentia the SAR terminal. Although the cellular infinition. Therefore, it is more plausible that blockade of $CO₂$ hydration after the administration of a CA inhibitor acts to depolarize hyperpolarization of the membrane potential of the SAR terminal. Although the CO_2 hydration after the administration of a CA filmotor at to depolarize hyperpolarization of the membrane potentia
the SAR terminal. Although the cellular mechanism med
ing the mechanosensitivity of SAR endings has to depoiarize hyperpoiarization of the membrane potential
the SAR terminal. Although the cellular mechanism medi
ing the mechanosensitivity of SAR endings has not yet be
determined, those receptors are believed to have str ing the mechanosensitivity of SAR endings has not yet been
determined, those receptors are believed to have stretch-
activated (SA) channels on the endings. In whole-cell patch-
clamp experiments using the labeled aortic b ing the mechanosensitivity of SAR endings has not yet been
determined, those receptors are believed to have stretch-
activated (SA) channels on the endings. In whole-cell patch-
clamp experiments using the labeled aortic b determined, those receptors are beneved to have stretch-
activated (SA) channels on the endings. In whole-cell patch-
clamp experiments using the labeled aortic baroreceptor neu-
rons in the nodose ganglion, Cunningham *e* cramp experiments using the labeled about barbieceptor heurons in the nodose ganglion, Cunningham *et al.* (1995) have demonstrated that the changes in conductance induced by hypoosmotic stretch appear to be mediated by an

Fig. 8. A) Light micrograph of the ex-**Fig. 8.** A) Light micrograph of the ex-
trapulmonary airways for CA activity
(×100). The erythrocytes of blood ves-Fig. 8. A) Light micrograph of the extrapulmonary airways for CA activity (\times 100). The erythrocytes of blood vessels show intense staining (arrow), but **Fig. 8.** A) Light micrograph of the extrapulmonary airways for CA activity (\times 100). The erythrocytes of blood vessels show intense staining (arrow), but smooth muscles (star) do not show stain-**Fig. 8.** A) Light micrograph of the extrapulmonary airways for CA activit $(x100)$. The erythrocytes of blood vessels show intense staining (arrow), busmooth muscles (star) do not show staining. B) Serial section of panel **Fig. 6.** A) Light micrograph of the extrapulmonary airways for CA activity (\times 100). The erythrocytes of blood vessels show intense staining (arrow), but smooth muscles (star) do not show staining. B) Serial section of smooth muscles (star) do not show staining. B) Serial section of panel A, incubated with 10^{-5} M acetazolamide, an in-
hibitor of CA. The erythrocytes of blood vessels are CA-negative (arrow). C) Light micrograph of the smooth muscles (star) do not show stain-
ing. B) Serial section of panel A, incu-
bated with 10⁻⁵ M acetazolamide, an in-
hibitor of CA. The erythrocytes of blood
vessels are CA-negative (arrow). C) Light
micrograph of t Ing. b) Senal section of panel A, incorded with 10^{-5} M acetazolamide, an inibitor of CA. The erythrocytes of blow
vessels are CA-negative (arrow). C) Lig
micrograph of the intrapulmonary a
ways for CA activity (×100). bated with 10 - M acetazolamide, an in-
hibitor of CA. The erythrocytes of blood
vessels are CA-negative (arrow). C) Light
micrograph of the intrapulmonary air-
ways for CA activity (×100). Lung epithe-
lial cells (arrow) vessels are CA-negative (arrow). C) Light
micrograph of the intrapulmonary air-
ways for CA activity (\times 100). Lung epithe-
lial cells (arrow) show intense staining,
but smooth muscles (star) do show any
significant stai micrograph of the intrapumonary air-
ways for CA activity (\times 100). Lung epithe-
lial cells (arrow) show intense staining,
but smooth muscles (star) do show any
significant staining. D) Serial section of
panel C, incubat lial cells (arrow) show intense staining,
but smooth muscles (star) do show any
significant staining. D) Serial section of
panel C, incubated with 10⁻⁵ M acet-
azolamide. Lung epithelial cells are CA-
negative (arrow). C

Fig. 9. Proposed model of the ion move-
ments for CO₂ hydration in an SAR ter-
minal.

chick heart (Hu and Sachs, 1994). Considering these obserthere is a close interaction between the Cl⁻ efflux and t
macroscopic mechanosensitive current has been reported
chick heart (Hu and Sachs, 1994). Considering these obser
vations, an intracellular Cl⁻ transport coupled there is a close interaction between the Cl⁻ efflux and the istr
macroscopic mechanosensitive current has been reported in inh
chick heart (Hu and Sachs, 1994). Considering these obser-
in t
vations, an intracellular Cl macroscopic mechanosensitive current has been reported in
chick heart (Hu and Sachs, 1994). Considering these observations, an intracellular Cl⁻ transport coupled to the Cl⁻ \leftrightarrow
Cl⁻ and Cl⁻ \leftrightarrow HCO₃ exchange s enck heart (11d and Saciis, 1334). Considering these costations, an intracellular Cl^- transport coupled to the Cl^-
 Cl^- and $Cl^- \leftrightarrow HCO_3^-$ exchange systems may be related
the functioning of the SA channels on the SAR endin vations, an intracellular Cl⁻ transport coupled to the Cl⁻ \leftrightarrow tensions and decreased pH levels in the tissue. In addition,
Cl⁻ and Cl⁻ \leftrightarrow HCO₃⁻ exchange systems may be related to acetazolamide has the effe the functioning of the SA channels on the SAR endings. **CO2 hydration in the** SAR terminals was blocked by admin-

istration of a CA inhibitor. As a generalized phenomenon, istration of a CA inhibitor. As a generalized phenomenon,
inhibition of CA activity is thought to elicit a disequilibrium
in the CO_2 transport system, giving rise to increased CO_2 istration of a CA inhibitor. As a generalized phenomenon,
inhibition of CA activity is thought to elicit a disequilibrium
in the CO_2 transport system, giving rise to increased CO_2
tensions and decreased pH levels in t istration of a CA inhibitor. As a generalized phenomenon
inhibition of CA activity is thought to elicit a disequilibriun
in the CO_2 transport system, giving rise to increased CO
tensions and decreased pH levels in the t istration of a CA inhibitor. As a generalized phenomenon,
inhibition of CA activity is thought to elicit a disequilibrium
in the CO₂ transport system, giving rise to increased CO₂
tensions and decreased pH levels in t in the CO_2 transport system, giving rise to increased CO_2
tensions and decreased pH levels in the tissue. In addition,
acetazolamide has the effect of decreasing the availability of
protons for Na⁺-H⁺ exchange. Bl densions and decreased pri levels in the ussue. In addition,
acetazolamide has the effect of decreasing the availability of
protons for $Na^+ \text{-} H^+$ exchange. Blockade of CA-dependent
 CO_2 hydration is also considered to protons for Na^+H^+ exchange. Blockade of CA-dependent CO_2 hydration is also considered to decrease pH in the SAR endings as well as in the vicinity of the endings, and this decrease in pH would inhibit the activity of $CO₂$ hydration is also considered to decrease pH in the SAR

1996
 whether intracellular or extracellular acidosis inhibits the Custretch sensitivity of mechanosensitive channels of SARs. 1996
whether intracellular or extracellular acidosis inhibits the
stretch sensitivity of mechanosensitive channels of SARs.
Fitzgerald (1940) observed that the discharge rate fron

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nether intracellular or extracellular acidosis inhibits the CUNNING

retch sensitivity of mechanosensitive channels of SARs.

Fitzgerald (1940) observed that the discharge rate from FITZGERA

why adapting mechanorecep whether intracellular or extracellular acidosis inhibits the c
stretch sensitivity of mechanosensitive channels of SARs.
Fitzgerald (1940) observed that the discharge rate from
slowly adapting mechanoreceptors of the cat's whether intracellular or extracellular acidosis inhibits t
stretch sensitivity of mechanosensitive channels of SARs.
Fitzgerald (1940) observed that the discharge rate free
slowly adapting mechanoreceptors of the cat's vi **traction.** If such an effect elicits the discharge rate frequency and the discharge rate frequency and appling mechanoreceptors of the cat's vibrissae velocition. If such an effect elicits the CO₂-induced SAR inhibion, **the one of the cat's vibrissae was**

diminished by an increase in extracellular calcium concentration. If such an effect elicits the CO₂-induced SAR inhibi-

then, then one would expect that administration of calcium

c diminished by an increase in extracellular calcium concentration. If such an effect elicits the CO_2 -induced SAR inhibition, then one would expect that administration of calcium channel blockers, which are known to preve tration. If such an effect elicits the CO_2 -induced SAR inhibi-
tion, then one would expect that administration of calcium
channel blockers, which are known to prevent the influx of
calcium ions, at least in part inhibit the administration of calculation, then one would expect that administration of calculation
channel blockers, which are known to prevent the influx of
calcium ions, at least in part inhibits the inhibitory responses
of re calcium ions, at least in part inhibits the inhibitory responses
of receptors to inhalation of CO_2 gas mixtures. However, in
this study the administration of nifedipine, a potent L-sub-
type calcium channel blocker (Mil this study the administration of $\frac{1}{2}$ gas infinities. However, in
this study the administration of nifedipine, a potent L-sub-
type calcium channel blocker (Miller, 1987; Matsumoto *et al.*,
1993), had no effect on type calcium channel blocker (Miller, 1987; Matsumoto *et al.*, M_{A1}
1993), had no effect on CO_2 -induced SAR inhibition. Because
there is evidence that CO_2 inhalation for a short period does
not cause either bronchoc there is evidence that CO_2 inhalation for a short period does
not cause either bronchoconstriction or bronchodilation, the
results of this study suggest that inhibition of SARs by CO_2
is independent of the influx of c there is evidence that CO_2 inhalation for a short period does
not cause either bronchoconstriction or bronchodilation, the
results of this study suggest that inhibition of SARs by CO_2
is independent of the influx of c not cause either bronchoconstriction or bronchodilation, the
results of this study suggest that inhibition of SARs by CO
is independent of the influx of calcium ions into the receptit
terminals. However, further studies a results of this study suggest that inhibition of SARs by θ is independent of the influx of calcium ions into the recepterminals. However, further studies are needed to elucide effect of other calcium channel blocks, su independent of the influx of calcium ions into the receptive

In animals, However, further studies are needed to elucidate

in effect of other calcium channel blocks, such as ω -cono-

in, on the mechanism of CO₂-indu

Hering-Breuer inflation reflex to terminate inspiration.

The effect of other calcium channel blocks, such as ω -cono-

toxin, on the mechanism of CO_2 -induced SAR inhibition.

Hering-Breuer inflation reflex to termina means for the mechanism of $\overline{O_2}$ -matted SAR infinition.
In anesthetized animals, the SARs are responsible for the
Hering-Breuer inflation reflex to terminate inspiration and
to prolong expiration, and the receptors h Hering-Breuer inflation reflex to terminate inspiration and
to prolong expiration, and the receptors have prominent
mechanisms for regulating the depth and rate of breathing
(Coleridge and Coleridge, 1986). The strength of Hering-Breuer inflation reflex to terminate inspiration and
to prolong expiration, and the receptors have prominent such the
mechanisms for regulating the depth and rate of breathing
(Coleridge and Coleridge, 1986). The s to prolong expiration, and the receptors have prominent
mechanisms for regulating the depth and rate of breathing
(Coleridge and Coleridge, 1986). The strength of the Hering-
Breuer inflation reflex would therefore be exp official during the depth and rate of breathing

(Coleridge and Coleridge, 1986). The strength of the Hering-

Breuer inflation reflex would therefore be expected to be

reduced by CO₂-induced SAR inhibition. Indeed, the reduced by CO_2 -induced SAR inhibition. Indeed, the duration

of inspiratory inhibition during lung inflation is increased by

of inspiratory inhibition during lung inflation is increased by

inhalation of hypercapnic ga of inspiratory inhibition during lung inflation is increased by of inspiratory inhibition during lung inflation is increased by
inhalation of hypercapnic gas mixtures (Bouverot *et al.*, 1970;
Younes *et al.*, 1974). Furthermore, the increase in SAR ac-
tivity is known to reduce the ef inhalation of hypercapnic gas mixtures (Bouverot *et al.*, 1974).

Younes *et al.*, 1974). Furthermore, the increase in SAR a

tivity is known to reduce the efferent vagal excitatory activit

to airway smooth muscle (Widdi tivity is known to reduce the efferent vagal excitatory activity
to airway smooth muscle (Widdicombe and Nadel, 1963),
which indicates that SARs can optimize the conflicting influ-
ences of dead space and airway resistance tivity is known to reduce the efferent vagal excitatory active to airway smooth muscle (Widdicombe and Nadel, 196 which indicates that SARs can optimize the conflicting inferences of dead space and airway resistance on al to airway smooth muscle (Widdicombe and Nadel, 1963),
which indicates that SARs can optimize the conflicting influ-
ences of dead space and airway resistance on alveolar venti-
lation. From the standpoint of bronchomotor which indicates that SARs can optimize the conflicting influences of dead space and airway resistance on alveolar ventilation. From the standpoint of bronchomotor activity, inhibition of SARs by CO_2 inhalation would imp

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