Nasal 'Pressure' Receptors

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ABSTRACT. This study was performed to identify, recording from single fibers of the ethmoidal nerve, nasal receptors which respond to changes in the upper airway pressure during nasal occlusion. In 15 anaesthetized rats breathing through the nose, three consecutive nasal occlusions were performed while recording the afferent activity of ethmoidal nerve fibers, the EMG activity of an external intercostal muscle, temperature in the nose and upper airway pressure. Twenty-two afferent fibers were activated during the three inspiratory efforts with occlusions applied at end-expiration, when the upper airway was subjected to negative pressure (−1.93, −2.16 and −2.22 kPa at the 1st, 2nd and 3rd effort, respectively). The number of impulses was 24, 22 and 20 (n=22) at the 1st, 2nd and 3rd effort, respectively. The pressure threshold were measured as −0.73, −0.87 and −0.96 kPa (n=22) in each effort. Three fibers were also stimulated by positive pressure during occlusions performed at end-inspiration. In 5 rats breathing through a tracheostomy, maintained negative (−0.1~3.7 kPa) and positive (0.8~3.0 kPa) pressures were applied to the isolated upper airway. All the 12 fibers tested were activated by the maintained negative pressure, whereas three of them were also activated by the maintained positive pressure. However, none of fibers tested were stimulated by tracheal occlusions. These results indicate that the ethmoidal branch of the trigeminal nerve contains fibers connected to nasal 'pressure' receptors, mostly 'negative pressure' receptors, that may play a role in the maintenance of upper airway patency.—KEY WORDS: nasal occlusion, nasal receptor, nose, pressure, trigeminal nerve.

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The upper airway is recognized as an important source of various respiratory reflexes such as sneezing, sniffing, coughing, apnea and bronchomotor action etc. and these reflexes are significantly related to the defense mechanism of airway [15]. Therefore, physiological studies on upper airway receptors, as well as tracheal and bronchial receptors, are essential to clarify such respiratory defense mechanisms; particularly, experimental data on nasal receptors have been desired [15, 16].

Negative pressure in the upper airway reflexly causes increased respiratory activity of upper airway dilating muscles such as alae nasi, genioglossus and posterior cricoarytenoid muscles (PCA) [4, 14]. This reflex contributes to maintain upper airway patency during normal breathing and protect the upper airway from collapse in the face of upper airway obstructions [3, 5, 10, 14].

Nerve endings sensitive to pressure changes in the upper airway have been known to exist in the larynx of the dog [1, 5, 9] and rabbit [8, 12] as well as in the pharynx of the cat [2]. These endings play an important role to elicit upper airway respiratory reflexes since a block of the superior laryngeal nerve (SLN) afferents or topical anesthesia of the larynx has largely reduced the reflexes to negative pressure in the upper airway [6, 10, 14].

The present study shows the rat nasal 'pressure' receptors which were activated by pressure changes in the upper airway when nasal breathing was briefly interrupted or the isolated upper airway was exposed to

maintained negative and positive pressures.

MATERIALS AND METHODS

Animals and anesthesia: Twenty Wistar male rats aged between 13 and 20 weeks were anesthetized with a mixture of urethane (1 g/kg, i.p.) and α-chloralose (0.1 g/kg, i.p.). If necessary, a further dose of urethane (0.5 g/kg) and α-chloralose (50 mg/kg) was injected intraperitoneally to maintain a surgical level of anesthesia.

Surgical procedure: In all experiments, a facemask (volume=2 m*l*) with two openings was constructed around the muzzle and sealed with quick-setting epoxy in order to apply nasal occlusions in rats breathing through the nose or maintained pressures to the isolated upper airway in rats breathing through a tracheostomy.

Impulses from afferents of the anterior ethmoidal nerve, a branch of the trigeminal nerve, were recorded in all experiments. The left ethmoidal nerve was identified near the anterior ethmoidal foramen through which the nerve re-enters into the cranial bone at the bottom of the orbit. The ethmoidal nerve was sectioned centrally and its peripheral cut-end was separated from the surrounding connective tissue with the aid of a binocular microscope. The ethmoidal nerve was desheathed and, in the case of recordings of single unit activity, split into several thin filaments from which action potentials were recorded. These nerve preparations were performed within the orbital cavity that was filled with warmed paraffin oil. The right ethmoidal nerve was left intact in all animals.

In experiments with tracheostomy breathing, both an upper airway cannula and a tracheal cannula were inserted into the trachea after the cervical trachea was longitudinally exposed in order to apply maintained pressures to the isolated upper airway.

Reordings of action potentials and other signals: In all rats single fiber or multi-fiber action potentials were recorded by a pair of platinum electrodes connected to a low-noise DC-preamplifier (DIA MED., DPA 201) and a biophysical amplifer (DIA MED., DPA100F).

The electromyogram (EMG) of the external intercostal muscle in the 4th intercorstal space was recorded with a pair of enamel-coated wires. The EMG activity was amplified with a biophysical amplifier and integrated (time constant=0.1 sec).

Pressure changes (P mask) in the face mask were detected with a pressure transducer (Toyoda, PD104) connected to a side opening of the facemask and amplified with a DC-amplifier (Toyoda AA3000).

Temperature change in the nasal cavity was also recorded during normal nasal breathing and during nasal occlusions using by a fine thermocouple probe (SENSOR-TEK IT-23, 0.23 mm in the tip diameter and 0.005 sec in time constant) attached to a thermometer (Bailey, BAT-12).

All these signals were displayed on a 4ch.-Braun tube oscilloscope (National, VP5403A), and the action potentials were also aurally monitored by means of a loud-speaker. In addition, all data were stored on a magnetic tape recorder (TEAC, MR-30) at a high speed of 38 cm/sec. When necessary, this was played back and recorded by a pen-writing oscillograph (San-ei, 8K21 or 8S).

Nasal occlusions: In fifteen rats breathing through the nose, nasal occlusions were performed by occluding the frontal opening of the facemask for three consecutive breaths at end-expiration or end-inspiration. The occlusion at end-expiration provided negative pressure in the upper airway due to an inspiratory effort while stopping airflow through the nose. On the other hand, the occlusion at end-inspiration produced positive pressure in the upper

airway due to a prolongation of lung inflation, i.e., Hering-Breuer inflation reflex.

Maintained pressures in the upper airway: In five rats breathing through a tracheostomy, negative (−0.1~3.7 kPa) and positive (0.8~3.0 kPa) pressures were applied to the isolated upper airway by using a 5 m*l*-syringe connected to the upper airway cannual while occluding the opening of the facemask.

Tracheal occlusion: The effect of tracheal occlusion was examined in rats breathing through a tracheostomy in which the opening of the tracheal cannula was obstructed at end-expiration for three to five respiratory cycles. This occlusion produced an augmentation of inspiratory activity in nasal muscles as well as in other respiratory muscles in the absence of nasal airflow and upper airway pressure changes.

Data analysis: The number of impulses of 'pressure' receptors was calculated during three consecutive nasal occlusions. Moreover, upper airway pressure (pressure threshold) which initiated impulses was measured together with peak pressure and the time of inspiration (T_I) during the nasal occlusion.

On these values, statistical analysis (Wilcoxon signed rank test) was used for comparisons between the first and 2nd or 3rd effort.

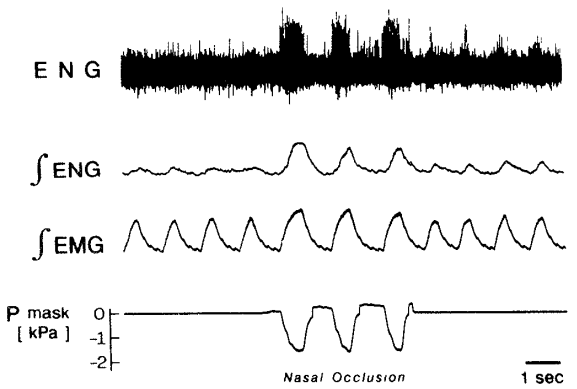

Fig. 1. Multi-fiber activity of the ethmoidal nerve during nasal occlusion. Note that ENG activity increased during three consecutive nasal occlusions. ENG: electroneurogram recorded from the ethmoidal afferent nerve. ∫ENG: integration of electroneurogram. ∫EMG: integration of electromyogram recorded from an external intercostal muscle. P mask: intra-mask pressure (upper airway pressure).

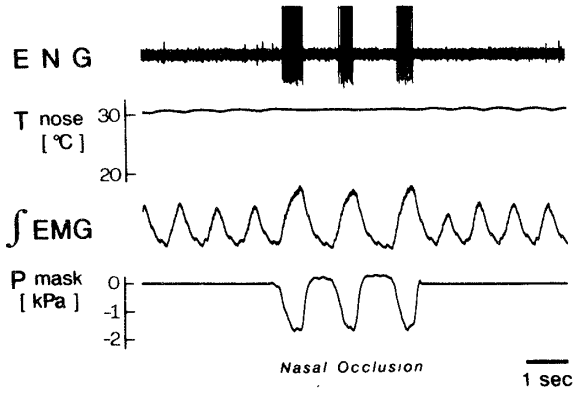

Fig. 2. Single unit activity of the ethmoidal nerve during nasal occlusion. T nose: intranare temperature. Other abbreviations are the same as in Fig. 1.

RESULTS

In order to perform the nasal occlusion, the opening of facemask was occluded at end-expiration for three breaths in rats breathing through the nose (Figs. 1, 2 and 3).

Multi-fiber activity of the ethmoidal nerve (ENG) was markedly increased by nasal occlusion in which the upper airway was subjected to negative pressure (P mask) (Fig. 1). The peak pressure ranged from −0.86 to −3.12 kPa during the three inspiratory efforts. Augmentation of the inspiratory muscle activity (EMG) was observed during these efforts.

Single unit activities were recorded from twenty-two afferent fibers responding to nasal occlusions. An example of these records was shown in Fig. 2. Impulses occurred during negative pressure swings in the upper airway pressure (P mask) while occluded at end-expiration. During the three consecutive nasal occlusions, pressure threshold whch initiated impulses varied

from −0.02 to −1.68 kPa, −0.08 to −1.58 kPa and −0.06 to −1.85 kPa at the 1st, 2nd and 3rd inspiratory effort, respectively. Another example of the records was shown in Fig. 3. Impulses were evoked by negative pressure (left panel) in which breathing was stopped at end-expiration but not by positive pressure (right panel) where breathing was stopped at end-inspiration.

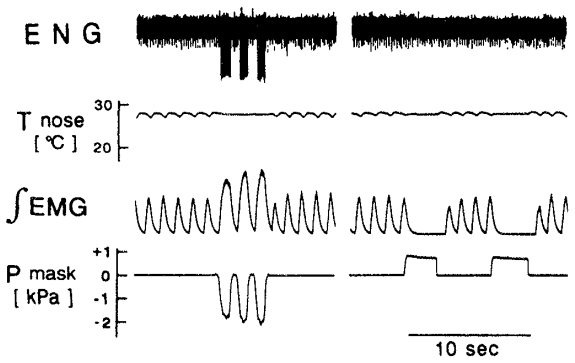

Fig. 3. Single unit activity of the ethmoidal nerve during nasal occlusion. Nasal occlusion was performed at end-expiration (left panel) or at end-inspiration (right panel). Abbreviations are the same as in Figs. 2 and 3.

All the 22 fibers did not show any activity till the nose was occluded. Although the vast majority of these fibers were not stimulated by positive pressure, only three fibers (3/22, 13.6%) were stimulated by both negative and positive pressure. However, the response to the positive pressure was very weak where only a few impulses occurred at the beginning of positive pressure.

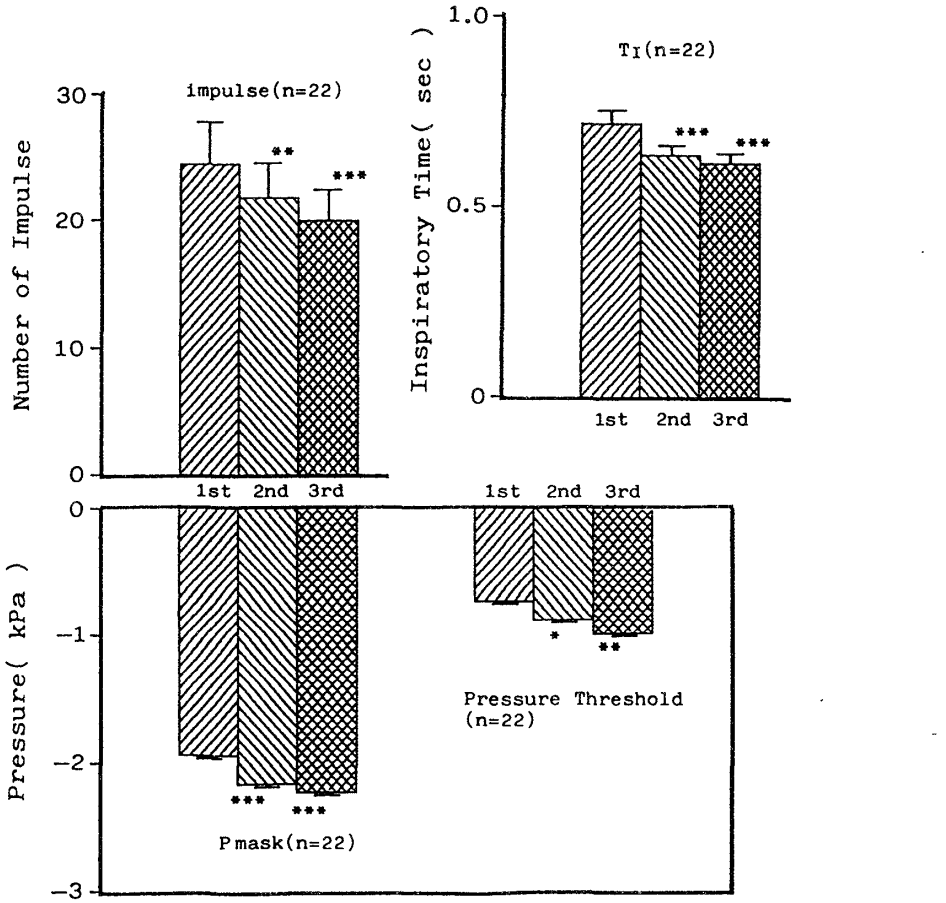

Fig. 4. Changes in number of impulse, inspiratory time (T_I), peak upper airway pressure and pressure threshold during three consecutive nasal occlusions. Each bar represents mean ± S.E. Asterisks: Differences are significant (Wilcoxon signed rank test, compared with the 1st occlusion). *: $0.01<P<0.05$. **: $0.005<P<0.01$. ***: $P<0.005$.

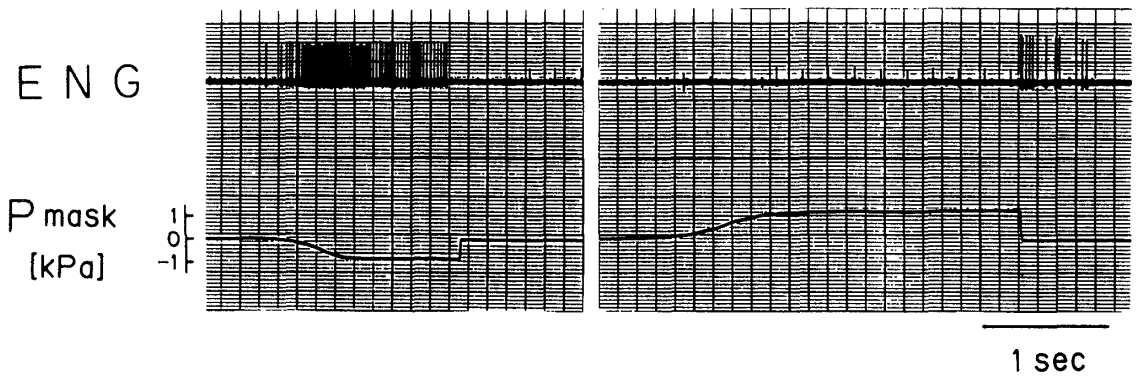

Fig. 5. Single unit activity of the ethmoidal nerve during maintained pressure applied to the isolated upper airway. Negative and positive pressures were applied in the left and right panels, respectively. Abbreviations are the same as in Fig. 1.

A summary of results from the twenty-two afferent fibers responsive to negative pressure during three consecutive nasal occlusions was shown in Fig. 4. The mean number of impulses tended to decrease, i.e., 24, 22 and 20 ($P<0.01$ or $P<0.005$), whereas the amount of change in upper airway pressure progressively increased, i.e., -1.93, -2.16 and -2.22 kPa ($P<0.005$) at the 1st, 2nd and 3rd inspiratory effort, respectively. The mean inspiratory time (T_I) was maximum at the 1st occlusion and decreased in the following two occlusions ($P<0.005$). Mean pressure threshold showed -0.73, -0.87 and -0.96 kPa at the 1st, 2nd and 3rd inspiratory effort, respectively ($P<0.05$, $P<0.01$).

In rats breathing through a tracheostomy, maintained negative ($-0.1\sim-3.7$ kPa) and positive (0.8~3.0 kPa) pressures were applied to the isolated upper airway. All the 12 fibers tested were clearly stimulated by the maintaned negative pressure (left panels in Figs. 5 and 6). The majority of these fibers were inactive to the maintained positive pressure (right panel in Fig. 5), whereas only three fibers (3/12, 25%) were responsible for the positive pressure. In some fibers, a small number of impulses were induced immediately after the termination of the maintained positive pressure (right panel in Fig. 5).

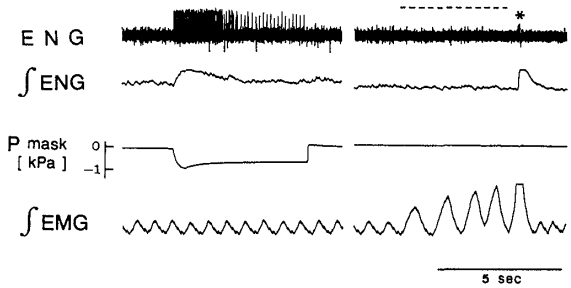

Fig. 6. Single unit activity of the ethmoidal nerve during maintained pressure and tracheal occlusion. In the left panel maintained negative pressure was applied to the isolated upper airway, and in the right panel tracheal occlusion was performed for four breaths. Asterisk in the right panel shows a fluctuation in ENG record due to a movement of body and thereby alarge change in the integrated ENG. Abbreviations are the same as in Fig. 1.

These fibers were tested for their response to tracheal occlusion, when the end of tracheal cannula was closed at end-expiration. All the fibers were not stimulated by this tracheal occlusion, while the rat was subjected to the strong inspiratory effort in the absence of pressure changes and flow in the upper airway (right panel in Fig. 6).

DISCUSSION

Pressure, flow (or temperature) and drive (or respiratory muscle activity) have been thought as major elements to stimulate sensory endings in the respiratory mucosa

and/or submucosa in the upper airway [7]. In fact, some nervous receptors associated with these sensory stimuli have been recorded in the dog larynx; 'pressure' receptors, 'cold' or 'flow' receptors and 'drive' receptors [1, 5, 9, 11, 16]. Receptors analogous to the laryngeal 'pressure' receptors of the dog have been found in the larynx of the rabbit [8, 12] and the pharynx of the cat [2].

In general, it has been recognized that negative pressure across the upper airway is a potent stimulus to such sensory endings [7, 16], although exceptionally in the rabbit positive pressure is a predominant stimulus in activation of the SLN afferents of which response is largely derived from the base of epiglottis [12].

Animal experiments have shown that the upper airway occlusion at end-expiration provoked a significant augmentation in the activity of upper airway dilating muscles, alae nasi, PCA and genioglossus muscles together with a prolongation of T_I, a decrease in the mean inspiratory slope (peak diaphragmatic activity/T_I) and a slowing of respiratory timing [3, 4, 7, 10, 14]. These respiratory reflexes were greater in the upper airway occlusion than tracheal occlusion, suggesting that the sensory endings in the trigeminal, glossopharyngeal and superior laryngeal nerves significantly participate with these reflexes. The enhanced activity of upper airway muscles was also induced by the maintained negative pressure applied to the isolated upper airway consisting of the nose, oropharynx and larynx, whereas the inspiratory activity of diaphragm and chest wall muscles was inhibited or not largely affected [4, 7, 14]. All these reflexes contribute in maintaining upper airway patency, i.e., regulating airway resistance, and in protecting the upper airway from collapse when the upper airway is obstructive [4, 10, 14]. Therefore, it would be particularly important that the presence of endings sensitive to pressure changes in the upper airway is demonstrated and their firing characteristics are extensively studied.

In this study, the author identified the trigeminal nasal receptors responding to the upper airway pressure change during nasal occlusion. All these receptors were remarkably stimulated by negative pressure but not by positive pressure, hence, almost of them were categorized as 'negative pressure' receptors.

In the nose of the rat, antother type of receptor has been reported as nasal 'flow' receptors of which spontaneous activity was markedly stimulated by cooling and inhibited by warming to the nasal cavity [13]. The primary mechanism to stimulate such receptors was evaporative heat loss on the surface of nasal passage. Moreover, their spontaneous activity was prevented by nasal occlusion when stopping airflow through the nose. A great number of nasal receptors (40/73, 57%) seemed to belong this group of 'flow' receptors [13]. The occurrence of nasal 'pressure' receptors in this study was not able to be decided since only the receptors sensitive to pressure changes were selected and recorded, though the rate of 'pressure' receptors was expected to be less than that of 'flow' receptors.

None of nasal 'pressure' receptors showed their activity till the nose was subjected to the obstruction or maintained pressures. The lack of spontaneous activity in these receptors is quite inconsistent with the findings obtained from the laryngeal pressure receptors in the dog [5] and also in the rabbit [12]. This discrepancy between the nasal and laryngeal 'pressure' receptors may be accounted for by the difference in their locations in the upper airway: The nasal receptors are located in the site near ambient air, thus, they would be minimally influenced by pressure change during normal nasal breathing. Mean pressure threshold to excite these receptors was -0.73 kPa at least. This pressure level

would hardly occur in normal nasal breathing, indicating that these receptors less contribute to the respiratory reflex in normal respiration but largely recruit in nasal obstruction. However, this is not necessarily associated with that all these receptors can be activated only by the large change in intranare pressure since some receptors were responsible for small negative pressure as low as −0.02 kPa.

Tracheal occlusion did not stimulate the nasal 'pressure' receptors. This proves that the activation of pressure receptors during nasal occlusion was essentially due to the pressure change in the nose but not an increased movement ('drive') of respiratory muscles such as alae nasi. Indeed, this is further ensured by the experiment that maintained negative pressure applied to the isolated upper airway markedly stimulated the receptor activity in the absence of inspiratory effort and flow.

In this study, the activity of nasal 'pressure' receptors tended to decrease during three consecutive occlusions despite the amount of peak upper airway pressure (P mask) increased progressively. This may depend on the progressive shortening of T_I of which duration indicates the length of negative phase in the upper airway pressure. Furthermore, there is another possibility that in some extent the receptors may adapt to pressure change by the repetition of nasal occlusion because the threshold became progressively higher, i.e., −0.73, −0.87 and −0.96 kPa in the 1st, 2nd and 3rd occlusion, respectively.

The mechanism by which 'pressure' receptors are stimulated has not been clarified in detail. However, one speculation is that the distortion of mucosa to which pressure transmitted and thereby stretching the endings is the exciting mechanism. Though the nasal mucosa and nasal vestibule are anatomically lined with nasal bone and cartilages, these sites would be distortable during nasal occlusion.

It has been known that the origin of upper airway reflexes largely depends on the SLN afferents [7]. However, in the case of nasal obstruction the trigeminal nerve also might conduct afferent informations about pressure changes in the nose and be related to the reflex augmentation of the respiratory muscle activity, particularly alae nasi. This may be supported by the finding that topical anesthesia on the nasal mucosa partly reduced respiratory reflexes to negative pressure applied to the upper airway [14].

This study elucidated that the ethmoidal branch of the trigeminal nerve contains fibers connected to nasal 'pressure' receptors, mostly 'negative pressure' receptors, that may play a role in the maintenance of upper airway patency.

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要　　約

鼻の'圧'受容器に関して：局　博一(東京大学農学部獣医環境生理学教室)一篩骨神経の単一神経活動の記録により，上気道の圧力変化を感知する鼻受容器の存在を見い出した．麻酔下の鼻呼吸ラット(15匹)及び気管呼吸ラット(5匹)において，篩骨神経の求心性活動，外肋間筋筋電図，鼻腔内温度及び上気道圧を同時記録した．鼻呼吸ラットでは呼気終末時に鼻マスクを3呼吸分閉鎖することにより実験的鼻閉塞を作出した．鼻閉塞時に上気道は3回の吸気努力に伴って平均−1.93～−2.22 kPa (n=22)の陰圧を生じたが，合計22本の求心性線維がこのような陰圧刺激に応答した．それぞれの吸気努力時におけるインパルス数は平均24～20 (n=22)を示し，インパルスを誘発する閾値は平均−0.73～−0.96 kPa (n=22)であった．鼻閉塞を吸気終末時に起こした場合には上気道に陽圧が生じたが，3本の線維のみが陽圧刺激にも応答した．気管呼吸ラットでは，上気道に外部から持続圧(陰圧，−0.1～−3.7 kPa; 陽圧，0.8～3.0 kPa)を与えた．12本の神経線維が陰圧刺激に応答し，そのうち3本は陽圧刺激にも応答した．記録した全ての線維は気管閉塞によっては刺激されなかった．これらの成績から，三叉神経の分枝である篩骨神経中に鼻腔内の圧力変化を感知する'圧'受容器が存在し，それらは大部分'陰圧'受容器であることがわかった．