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Evidence for Passing Down of Postnasal Drip into Respiratory Organs

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Abstract. *Postnasal drip is believed to be one of the main sources of serious respiratory diseases, such as sinobronchial syndrome. However, there is little direct evidence showing that postnasal drip flows into the trachea and results in the development of inflammatory responses in the lower airway. In the present study, whether postnasal drip entered the respiratory organs and whether material in the trachea moved toward the lungs and the digestive organs were examined by using an experimental model with mice. Materials and Methods: In the first set of experiments, 1.0 μL of ^{51}Cr-labeled pseudo-postnasal drip in a normal saline or a glycerin solution was instilled into the nasal cavity of male ICR mice anesthetized with sodium barbital by intraperitoneal injection. In the second set of experiments, the destination of ^{51}Cr-labeled red blood cells (RBCs) after intratracheal instillation was examined in the anesthetized mice. The lungs, the stomach and the intestines were removed from mice killed under anesthesia at various intervals after instillation, and measured for radioactivity. Results: When glycerin solution containing ^{51}Cr (but not normal saline) was instilled in mice, the presence of much higher levels of ^{51}Cr was observed in the lungs. Although the presence of high levels of ^{51}Cr-labeled RBCs was observed in the lungs one hour after instillation radioactivity in the lungs gradually decreased as time went by. On the other hand, radioactivity in the digestive organs gradually increased and peaked three hours after instillation with ^{51}Cr-labeled RBC. Conclusion: These results suggest that thicker viscous postnasal drip can flow into the respiratory organs when the host is asleep. In addition, postnasal drip which flows into the trachea can move gradually to the oral side by mucociliary transportation of the tracheal mucosa and thus be swallowed.*

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A number of studies have been performed to examine the relationship between diseases in the upper and the lower respiratory tracts, reporting positive correlations between them (1-5). In particular, the chronic inflammatory lesions that coexist in the upper and the lower respiratory tracts are called sinobronchial syndrome (SBS). SBS is defined as a coexisting pathology of chronic rhinosinusitis and a non-specific chronic inflammatory lesion of the lower respiratory tract such as chronic bronchitis, bronchiectasis, or diffuse panbronchiolitis. Although SBS has been frequently reported, the precise mechanisms of the development of SBS are not well defined.

Many reports proposed that a downward progression, an upward progression, or constitutional causes are responsible for the development of SBS (6). It is also hypothesized that sinusitis occurs firstly and then this inflammation progresses downward to develop into bronchial diseases. This hypothesis is called the "pus aspiration theory" and, in this theory, flowing postnasal drip into the trachea is believed to play a pivotal role in the development of the diseases (7-9). However, there is little direct evidence showing that postnasal drip flows into the trachea and results in the development of inflammatory responses in the lower airway (10). Therefore, the present study was undertaken to examine the flow of postnasal drip into the respiratory organs. Furthermore, the destination of postnasal drip in the trachea was experimentally examined.

Materials and Methods

Mice. ICR male mice, 7 to 8 weeks of age, were purchased from Charles River Japan Inc. (Atsugi, Japan). The animals were maintained on a 12-hour light/dark cycle with constant temperature (25±2˚C) and relative humidity (55±5%) with normal mouse chow and tap water *ad libitum*. All experimental procedures were approved by the Animal Care and Use Committee of Showa University and were carried out in accordance with the guidelines of the Physiological Society of Japan.

Preparation of radio-labeled red blood cells. Mice were anesthetized with intraperitoneal injection with 50 mg/mL of sodium pentobarbital (Abbott Laboratories, North Chicago, IL, USA) in a volume of 0.3 mL. Mice were then bled by cardiac puncture in the presence of 0.1 mL of heparin (Novo Nordisk A/S, Copenhagen, Denmark). The blood was then centrifuged at 1,500 xg for 15 min at 4˚C, and plasma was removed. The remaining cell pellets were washed three times with phosphate-buffered saline (PBS) by centrifugation (1,500 xg for 15 min at 4˚C), and suspended in Medium 199 (GIBCO BRL, Grand Island, NY, USA) at a concentration of 5×10^{10} cells/mL. The red blood cells (RBCs) were incubated with 500 μCi of sodium chromate-51 (^{51}Cr, specific activity: 683.15 mCi/mg; NEN Corp., Boston, MA, USA) for 2 hours at 37˚C. RBCs were then washed 5 times with PBS, suspended in PBS at 10% and used as ^{51}Cr-labeled RBC.

Preparation of pseudo-postnasal drip. ^{51}Cr (NEN Corp.) was added to 1.0 mL of both normal saline and glycerin in a volume of 0.1 mL, well mixed and used as ^{51}Cr-labeled pseudo-postnasal drip.

Assay for flow of postnasal drip. To examine the flow of postnasal drip into respiratory organs, 1.0 μL of the ^{51}Cr- labeled pseudo-postnasal drip was instilled into the nasal cavity of mice anesthetized by intraperitoneal injection with 0.5 mg sodium pentobarbital (Abbott Laboratories). To mimic the sleeping state of a human being, the mice were injected intraperitoneally with 0.5 mg sodium pentbarbital (Abbott Laboratories) every 3 hours for 12 hours. The mice were then killed by cervical dislocation 1, 3, 6, 9, 12 and 24 hours after treatment, and radioactivity in the lungs was measured. In cases of examining the excretion of ^{51}Cr, mice were maintained in metabolic cages for one hour, and urine and feces were collected. The radioactivity of urine (0.1 mL) and feces (0.1 g) was measured in a similar manner.

Assay for destination of postnasal drip in the trachea. The mice were anesthetized as above and a middle incision was performed above the sternum. The trachea was exposed by blunt dissection, a 28-gauge needle was inserted into the trachea above the carina and 0.01 mL of 10% of ^{51}Cr-labeled RBCs was injected. These mice were killed by cervical dislocation 1, 2 and 3 hours after injection, and radioactivity in the lungs, the stomach and the intestines was measured.

Statistical analysis. Data are presented as the mean±SEM of five mice. The statistical significance of the data between the control and experimental groups was analyzed by Mann-Whiteny *U*-test. *P*-values of <0.05 were considered statistically significant.

Results

Flow of postnasal drip. The first experiment was undertaken to examine whether postnasal drip was able to flow into the respiratory organs. ^{51}Cr-labeled postnasal drip was instilled into the nasal cavity of mice and the radioactivity in the lungs was examined 1 to 24 hours after treatment. Radioactivity in the lungs obtained from mice instilled with normal saline was extremely low (Figure 1). On the other hand, instillation of glycerin into the nasal cavity caused flow of solution into the lungs. Radioactivity in the lungs peaked one hour after treatment and then decreased gradually (Figure 1). The reasons why radioactivity in the lungs decreased as time went by were therefore examined. To do this, mice instilled ^{51}Cr-labeled postnasal drip (glycerin) were maintained for one hour in metabolic cages, and feces and urine were collected separately for radioactivity examination. As shown in Figure 2, the radioactivity of urine collected 23 to 24 hours after instillation was significantly ($p<0.05$) higher than that collected 11 to 12 hours after instillation. The data in Figure 2 also clearly show the presence of much higher levels ($p<0.05$) of radioactive materials in feces collected 23 to 24 hours after instillation as compared with that collected 11 to 12 hours after instillation.

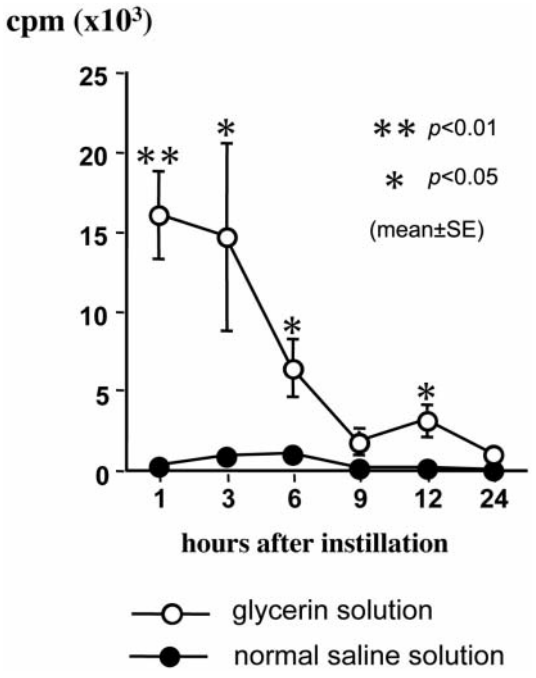

Figure 1. *The flow of pseudo-postnasal drip into the lungs.*

Destination of radio-labeled RBCs after intra-tracheal instillation. The third experiment was carried out to examine whether materials in the trachea could move toward the lungs and digestive organs. Mice instilled directly with ^{51}Cr-labeled RBCs into the trachea were killed 1, 2 and 3 hours after treatment, and radioactivity in the lungs, stomach and intestines was measured. Although the presence of high levels of ^{51}Cr-labeled RBCs was observed in the lungs obtained from mice one hour after instillation, radioactivity in the lungs gradually decreased as time went by (Figure 3A). On the other hand, radioactivity in the digestive organs, the stomach and the intestines gradually increased and peaked three hours after instillation with ^{51}Cr-labeled RBCs (Figures 3B, C).

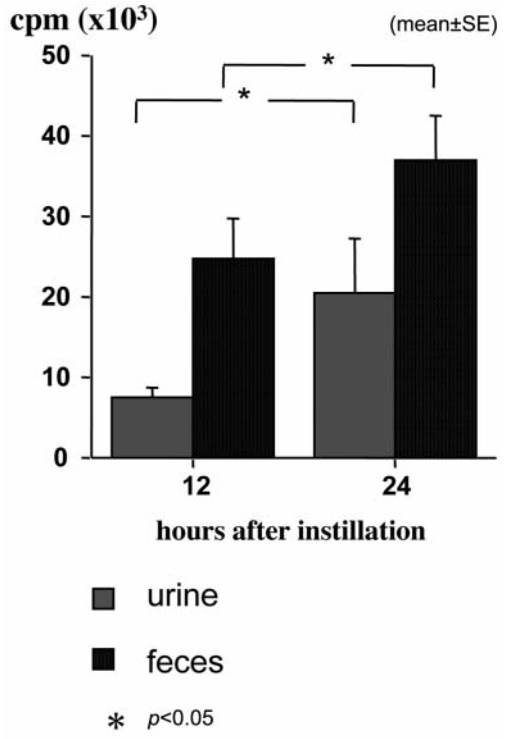

Figure 2. *The change of radioactivity of chromium 51 in urine and feces.*

Table I. *Etiological factors of sinobronchial syndrome.*

I.	Descending theory
	Aspiration of postnasal drip
	Via circulatory system
	Via lymphatic system
	Abnormal nasal respiration
	Nasopulmonary reflex
II.	Ascending theory
	Cough
	Via circulatory system
III.	Hereditary constitution
	Defective defense mechanism of the total airway system

Discussion

Chronic inflammation has been known to occur concurrently in both the upper and lower airways for a very considerable period. In the beginning of the 19th century, Láennec, the founder of stethoscopy, described in his diary his own suffering from cough accompanied by an obstinate postnasal drip and expectoration (11). Thomson (12) mentioned in 1914 that suppurative rhinosinusitis may cause obstinate bronchorrhea. Since then, diseases corresponding to what is now called SBS have been reported in terms of the relationship between the upper and lower airways.

The clinical symptoms of SBS include the symptoms of chronic rhinosinusitis such as rhinorrhea, postnasal drip, nasal congestion, loss of smell, and heavy feeling in the head accompanied by bronchial symptoms such as coughing, expectoration, shortness of breath on exertion and strider. It has been reported that bronchial symptoms improve if treatment of rhinosinusitis is effective (13-16).

Several theories about the pathogenesis of SBS have been presented, as shown in Table I. Most of the discussion has supported the aspiration of postnasal drip theory (5, 7-9, 17) and other theories assuming that lower airway lesions originate from rhinosinusitis and develop downwards. Upper airway infections could leave the patients with a persistent condition of catarrh and postnasal drip syndrome (18), due to some change in mucociliary clearance causing accumulation of mucus in the postnasal space (8). Quinn and Mayer (7) first reported that the lipiodol of contrast medium used in X-ray examinations, which had been inserted into the nasal cavities of sleeping subjects, was detected in the trachea. This observation was afterwards confirmed by McLaurin (1932), Nagoshi (1960) and Awataguchi (1962) (19). However, cases where lipiodol was actually detected in the trachea were few. Furthermore, there was a controversy regarding these results, because lipiodol has a different relative density than that of real postnasal drip in chronic rhinosinusitis. Thus, despite the fact that postnasal drip has been discussed as an important cause in SBS, it is still unclear if postnasal drip actually flows into the trachea. Therefore, normal saline or glycerin were used as an experimental model in the present study. The experiments have proven quantitatively that postnasal drip can flow into the respiratory organs.

When a solution of low viscosity such as normal saline solution, assumed to be nasal discharge in a healthy case, was used in the experiment of mice anesthetized with sodium pentobarbital, almost no postnasal drip flowed into the lungs. On the other hand, a solution of high viscosity such as glycerin, assumed to be nasal discharge in chronic rhinosinusitis, flowed into the lungs as shown in Figure 1. These results strongly suggest that entrance of postnasal drip into the trachea and the lungs may be owing to host conditions, such as whether the host is asleep or awake, and thicker viscous postnasal drip may easily enter the respiratory organs.

According to the animal experimental results, the following can be conceived as a possible mechanism in the case of a human being by which postnasal drip flows into the trachea. In a human being that is asleep, tonic contraction of the lower pharynx constrictor is found to occur. In addition, while sleeping, the lower pharyngeal space wall adheres to the larynx because of the different body position (supine position). For these two reasons, the entrance to the esophagus closes. It is also thought that the

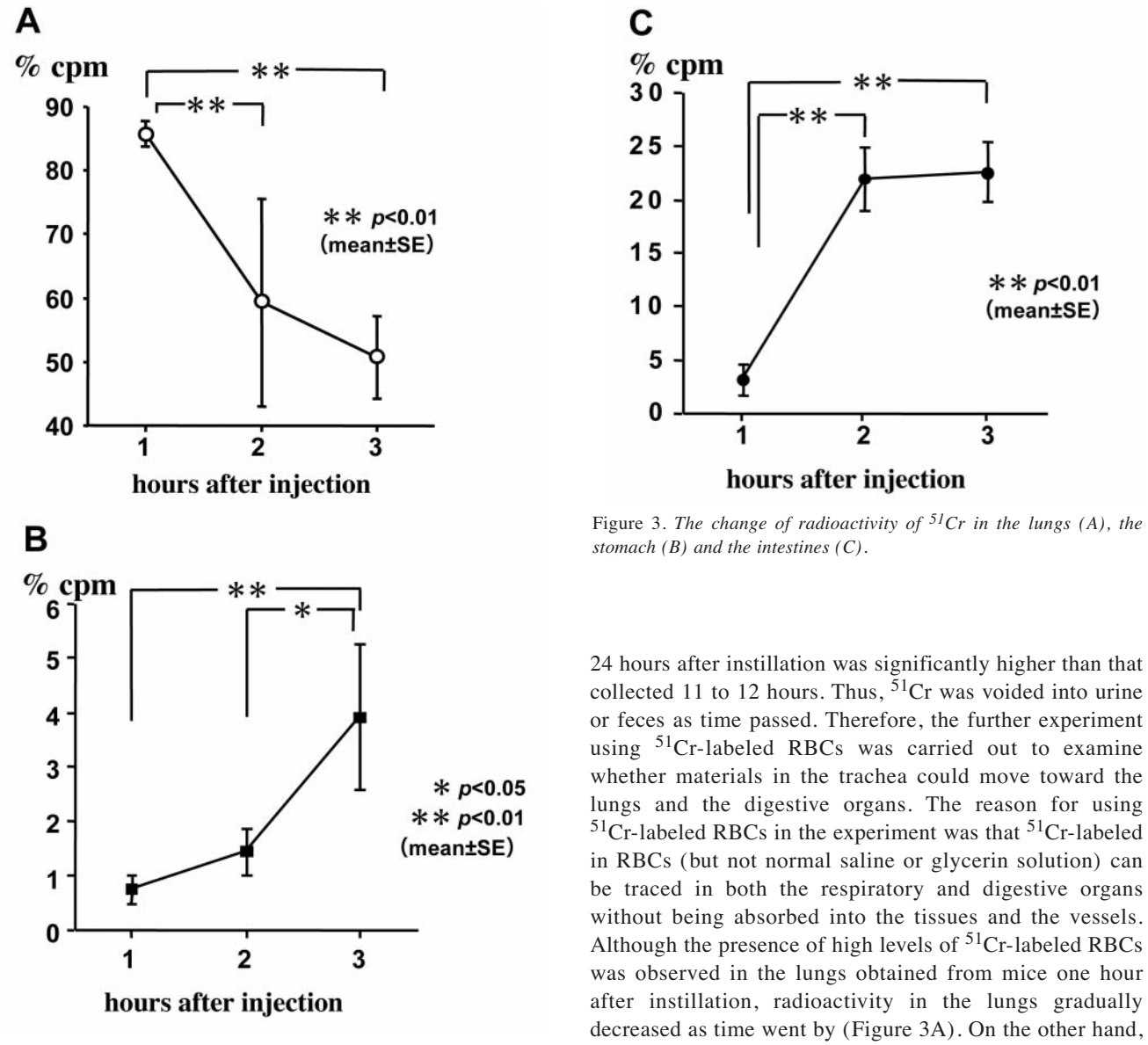

Figure 3. *The change of radioactivity of ^{51}Cr in the lungs (A), the stomach (B) and the intestines (C).*

swallowing reflex decreases, resulting in the accumulation of postnasal drip at the entrance to the esophagus. Sleeping produces a decrease in the coughing reflex, causing a secondary flow of postnasal drip into the trachea. It is further thought that higher viscosity makes it easier for postnasal drip to flow into the trachea by contributing to the afore-mentioned accumulation at the entrance to the esophagus. The postnasal drip accumulates for a longer time than when the viscosity is low, so that the secondary flow into the trachea can occur even when the human being is awake.

In this experiment, radioactivity in the lungs that attained a peak one hour after instillation of ^{51}Cr-labeled postnasal drip (glycerin) decreased as time went by. As shown in Figure 2, radioactivity in urine and feces collected 23 to 24 hours after instillation was significantly higher than that collected 11 to 12 hours. Thus, ^{51}Cr was voided into urine or feces as time passed. Therefore, the further experiment using ^{51}Cr-labeled RBCs was carried out to examine whether materials in the trachea could move toward the lungs and the digestive organs. The reason for using ^{51}Cr-labeled RBCs in the experiment was that ^{51}Cr-labeled in RBCs (but not normal saline or glycerin solution) can be traced in both the respiratory and digestive organs without being absorbed into the tissues and the vessels. Although the presence of high levels of ^{51}Cr-labeled RBCs was observed in the lungs obtained from mice one hour after instillation, radioactivity in the lungs gradually decreased as time went by (Figure 3A). On the other hand, radioactivity in the digestive organs gradually increased and peaked three hours after instillation with ^{51}Cr-labeled RBC (Figures 3B, C). From these results, it was suggested that ^{51}Cr-labeled RBCs instilled into the trachea moved gradually to the oral side by mucociliary transportation of the tracheal mucosa and were swallowed.

In conclusion, there is a possibility that viscous postnasal drip in a patient with rhinosinusitis flows into the trachea, especially during sleep. However, when mucociliary function of the lower airway mucosa is normally exerted, postnasal drip which flows into the trachea can move to the oral side and be swallowed. Therefore postnasal drip in rhinosinusitis can be a factor triggering inflammatory exacerbation in the lower airway, however, it cannot be concluded that postnasal drip is necessarily a factor causing initial inflammation in the lower airway.

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