Segmental Differentiation of Endothelial Intercellular Junctions in Intra-acinar Arteries and Veins of the Rat Lung

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SUMMARY The present study examines by freeze fracture the structure of endothelial intercellular junctions in pulmonary intra-acinar arteries and veins. Because of the complexity of the pulmonary vascular bed, it was necessary to devise a means to distinguish venous from arterial vessels in freeze fracture replicas. By modifying a recently described technique, which entails occluding venous outflow during intravascular perfusion fixation of the lung, the arteries were emptied of and the veins filled with erythrocytes. Tight junctions (TJ) of intra-acinar arteries, ranging in internal diameter from 17 to 125 μm, consisted of two to six continuous, interconnected rows of particles, 100-500 Å in length, present in grooves on the E face and complementary low, particle-poor ridges on the P face. Numerous large gap junctions (GJ) were present in the meshwork of TJ and formed rows parallel to the TJ elements. In intra-acinar veins, measuring 32-284 μm in internal diameter, TJ consisted of one to five sparsely interconnected rows of particles on the E face and low, virtually particle free ridges on the P face. Gap junctions were smaller and fewer in veins than in arteries. In both arteries and veins, "special endothelial junctions" were observed. These consisted of closely spaced, alternating rows of GJ and TJ particles and were similar to those observed in systemic vessels (Simionescu et al., 1976.) The presence of GJ suggests that there is extensive electrotonic and/or metabolic coupling in arterial endothelium, and that this is less extensive in venous endothelium. The continuous network of multiple TJ particles in both arteries and veins suggests that these segments are less permeable than the venular ones.

AS a consequence of the anatomic location of the lungs, pulmonary endothelial cells are exposed to the entire cardiac output, and are thereby well situated to perform the important function of metabolizing a number of biologically active materials (Fishman and Pietra, 1974). These cells also form a permeability barrier against the indiscriminate leakage of water-soluble macromolecules into the pulmonary interstitium (Taylor and Gaar, 1970; Schneeberger, 1976). A freeze fracture study of pulmonary capillaries has shown this to be due, in part, to the presence of one to three stranded tight junctions which, in the venular segment, have relatively few junctional particles, whereas, in the arteriolar portion, they are associated with small gap junctions (Schneeberger and Karnovsky, 1976). Although the structures revealed by freeze fracture are intramembranous in location rather than surface features of the junctions (Staehelin, 1974), the findings nonetheless suggested that junctions at the venular end should be more permeable than those at the arteriolar end of the pulmonary capillary bed. Furthermore, the presence of gap junctions indicated that endothelial cells in the arteriolar segment are likely to be electrotonically and/or metabolically coupled (Goodenough, 1980). These observations of lung capillaries are similar to those reported for the systemic capillary beds of mesentery and omentum (Simionescu et al., 1975).

Examination by freeze fracture of defined segments of the systemic vasculature has revealed that in vessels larger than capillaries there is also a distinct segmental differentiation of endothelial intercellular junctions (Simionescu et al., 1976). The complexity of the pulmonary vascular bed has thus far prevented the definitive identification of intra-acinar arteries and veins in freeze fracture replicas. This difficulty has now been overcome. By modifying a recently described method of intra-arterial perfusion fixation combined with simultaneous occlusion of the venous outflow (Meyrick and Reid, 1979), advantage was taken of the fact that red blood cells (RBC) became markers for intra-acinar veins leaving arteries empty. The present study was undertaken to establish by freeze fracture the structure of endothelial junctions in intra-acinar arteries and veins, and to compare it to those observed in systemic vessels.

Methods

Animals

Sixty female Sprague-Dawley rats (Charles River Breeding Laboratories, Inc.) weighing between 125 and 205 g were used in the present study. They
were housed in plastic cages supplied with filtered air, and the absence of pulmonary infection was confirmed by histological means.

**Fixation Procedure**

Fixative, consisting of 2% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.3, was introduced simultaneously into the trachea and into the pulmonary artery at 25 and 100 cm H2O pressure, respectively, while the venous outflow was occluded. To carry this out, the animal was first anesthetized with an intraperitoneal injection of sodium pentobarbital (Diabital, Diamond Laboratories, Inc.). 5 mg/100 g of body weight. After the trachea had been exposed, a loose ligature was placed around it. The thorax was opened by two lateral incisions in the anterior chest wall and the diaphragm cut. A portion of the thymus was removed to facilitate identification of the pulmonary artery. A small cut was made in the trachea and PE-100 polyethylene tubing (Clay Adams) from the tracheal fixative reservoir was tied into place. Occlusion of the pulmonary venous outflow was achieved by clamping the pulmonary veins with a hemostat, and the tubing of the vascular fixative reservoir was connected to the pulmonary artery by way of a 19-gauge needle. Flow from both reservoirs was begun at the same time. After 1 minute, both tubes were clamped simultaneously, and the trachea, heart, and lung were removed en bloc and immersed in the same fixative for an additional 20 minutes. They were then stored at 4°C in 0.15 M cacodylate buffer, pH 7.3.

Whereas an arterial perfusion pressure of 100 cm H2O exceeds the physiological range for the pulmonary capillary bed, it was found to be necessary in order to achieve a consistent clearing of arterial vessels of their contents. In a previous study using mouse lungs it was found that, while intravascular perfusion at a pressure of 140 cm H2O considerably distended pulmonary capillaries, it had no effect on the morphology of capillary endothelial junctions. (Schneeberger and Karnovsky, 1976).

**Light and Electron Microscopy**

Fragments of tissue from all lungs were post-fixed in 1% OsO4, with 15 mg/ml potassium ferrocyanide (Karnovsky, 1971) for 1 hour at 4°C. The tissue was stained en bloc with 1.5% uranyl acetate in 0.05 M maleate buffer, pH 6.2, dehydrated in graded ethanol, infiltrated, and embedded in Epon. Sections, 1 μm thick, were stained with toluidine blue and examined by light microscopy. For electron microscopy, thin sections were cut with a diamond knife (Balzers Union) on an LKB Ultrotome V (LKB) picked up on carbon-coated grids, stained with lead citrate, and examined in a Philips 301 electron microscope.

**Freeze Fracture**

Small pieces of lung, taken from the same areas which had been sampled for light and electron microscopy, were infiltrated with glycerol at concentrations increasing from 10 to 30% in 0.1 M cacodylate buffer, pH 7.3, for 2 hours at 4°C. The tissue then was frozen rapidly in liquid nitrogen cooled to −210°C under vacuum, and fractured in a double replica device at −115°C, using a Balzers BAF 400T high-vacuum freeze-etch unit (Balzers Corp.). The carbon-platinum replicas were washed in 5.2% sodium hypochlorite (Chlorox Co.), followed by distilled water, picked up on Formvar-coated 100 mesh copper grids, and examined in the electron microscope.

**Measurements**

Because, in freeze fracture replicas, it is not always possible to discern the necessary details to make accurate external diameter measurements, internal diameters were used instead. They were obtained by determining the minimum distance between the luminal membranes of opposite endothelial cells. The measurements were made either on electron micrographs at a final magnification of 4750X or directly in the electron microscope at a primary magnification of 1900X as follows: In the Philips 301 electron microscope, a circle, 4 cm in diameter, is inscribed on the fluorescent screen. At the above magnification, this represents 21 μm. The internal diameter of the vessel was determined by moving the image of the vessel sequentially past this fixed circle, noting how many times the diameter of the latter was contained within the vessel lumen.

**Results**

**Light Microscopy**

The following criteria were used to determine whether lungs were processed further for freeze fracture: (1) All arteries had to be completely devoid of RBC. (2) All veins had to be completely filled.
TABLE 1  Frequency of Occurrence of Endothelial Gap Junctions (GJ) and Tight Junctions (TJ) in Intra-acinar Pulmonary Arteries, and Veins as Determined by Transmission Electron Microscopy on Thin-Sectioned Vessels

<table>
<thead>
<tr>
<th>Type of vessel</th>
<th>Range of diameters* (μm)</th>
<th>No. of vessels examined</th>
<th>No. of junctions examined</th>
<th>% of junctions having GJ</th>
<th>TJ†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>26-125</td>
<td>25</td>
<td>49</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>Vein</td>
<td>30-147</td>
<td>32</td>
<td>56</td>
<td>18</td>
<td>56</td>
</tr>
</tbody>
</table>

* In order to compare these data with those derived from freeze fracture replicas, internal diameters were measured. This was obtained by measuring the minimum distance between the luminal membranes of opposite endothelial cells.

† This figure includes those junctions in which only tight junctions could be discerned, as well as those in which the presence of gap junctions implied the association of tight junction elements, as discussed under Methods and as based on the freeze fracture evidence.

Electron Microscopy of Thin Sections

Veins were readily distinguished from arteries by the presence of RBC and fixed plasma proteins in the lumen of the former and the absence of any fixed luminal material within the latter (Figs. 2, a and b, and 3, a and b). The chief distinguishing ultrastructural feature between the intercellular

with RBC (Fig. 1). Under such conditions, capillaries surrounding arteries tended to be empty and those surrounding veins contained RBC. Because these criteria were strictly adhered to, approximately half of the lungs were not processed for freeze fracture.

**Figure 1** Light micrograph showing the appearance of the lung following intravascular perfusion during venous outflow occlusion. All arterial vessels (arrow heads) are free of and all venous vessels (V) are filled with RBC. A bronchiole (B) is indicated. 160X.

**Figure 2** Electron micrographs of arterial and venous endothelial clefts in which there is a short endothelial cell overlap. Note that the lumen of the artery is empty, and that of the two veins contains fixed plasma proteins. The internal diameter of each vessel is indicated in parentheses. As discussed under Methods, it is assumed, based on the freeze fracture evidence, that tight junction elements flank the gap junctions even though they cannot be resolved in the present electron micrographs. a: Arterial junction in which there is a small gap junction (GJ) in the distal end of the cleft (107 μm). 102,000X. b: Venous junction with a small GJ in distal end of the cleft (62 μm). 62,700X. c: Venous tight junction (TJ) showing a single area of apparent fusion of the external leaflets of the adjacent unit membranes (37 μm). 102,000X.
junctions of arteries and veins was the greater frequency (Table 1) and usually larger size of gap junctions associated with the tight junctions of arteries (Figs. 2a and 3a). The presence of gap junctions was, however, not related to vessel size since they were seen in both arteries and veins ranging in internal diameter from 26 to 147 μm. Within any given vessel, the adjacent endothelial cells overlapped to a greater or lesser extent, resulting in intercellular clefts of varying depth. For example, in those cases in which there was no overlap, only a single, focal area of fusion of the outer leaflets of the adjacent unit membranes was usually observed (Fig. 2c). By contrast, in intercellular clefts in which there was extensive endothelial cell overlap, the resulting long, narrow intercellular spaces were interrupted by multiple punctate areas of fusion of the outer unit membranes (tight junctions) (Fig. 3c), and by lengthy areas where membrane fusions formed pentalaminar arrays (gap junctions) (Fig. 3, a and b). When gap junctions were present, it was not possible in thin sections to resolve the associated tight junction elements. Gap junctions, when present, were usually situated toward the abluminal end of the intercellular space. Between venous endothelial cells, the intercellular space was occasion-

![Image](http://circres.ahajournals.org/)

**Figure 3** Electron micrographs of arterial and venous endothelial clefts in which there is extensive overlap of adjacent endothelial cells. Internal diameters are indicated in parentheses. As indicated in Figure 2 and in Methods, it is assumed that tight junction elements are closely associated with those of the gap junctions, but they cannot be resolved in the present electron micrographs. a: Artery showing a large GJ in the middle of the cleft (41 μm). 88,000X. b: Vein showing unusually extensive GJs (70 μm). 88,000X. c: Vein in which the intercellular space is maintained over a long length and is interrupted by only two sites of apparent membrane fusion due to the presence of TJJs (147 mm). 88,000X.
ally maintained over long lengths, and was interrupted by only one or two punctate areas of membrane fusion representing the site of tight junctions (Fig. 3c).

Electron Microscopy of Freeze Fracture Replicas

The number of replicas examined is indicated in Table 2. The observations made on thin-sectioned vessels were confirmed in freeze fracture replicas: gap junctions were more numerous and larger between arterial than between venous pulmonary endothelial cells (Table 3). Furthermore, the mean and range of the number of rows of tight junction particles was somewhat higher in arteries than in veins (Table 2).

Arteries

Since it was not possible, in freeze fracture replicas, to distinguish between fully and partially muscularized arteries (Reid, 1979), the particular segment examined was identified by its internal diameter. The nonmuscular portion could be identified, however, because its internal diameter was larger than that of capillaries, the lumen was devoid of RBC, and smooth muscle cells could not be discerned below the endothelium. These criteria are similar to those used to identify, by light microscopy, the nonmuscular segments of intra-acinar arteries in developing and adult lungs (Reid, 1979).

In intra-acinar arteries, ranging in internal diameter from 30 to 125 μm, the intercellular junctions were characterized by the widespread presence of gap junctions within the meshwork of tight junctions. The latter formed an interconnected network of two to six rows of particles of varying (100-500Å) length present in E face grooves (Fig. 4a). On the P face, the low tight junction ridges contained few junctional particles and, instead, often displayed a narrow apical furrow (Fig. 4, b and c). In addition to forming, on the P face, irregular arrays of closely spaced gap junction particles measuring about 80Å in diameter (Fig. 4c), the latter also formed single and sometimes multiple rows of particles running parallel and in close proximity to tight junction grooves (Fig. 4b). On the E face, gap junction particles were revealed as closely packed complementary pits (Fig. 4a). Although the most frequently observed morphological organization was one of irregular patches of gap junction particles intercalated within the meshwork of the tight junction, in a number of areas, closely spaced alternating rows of tight and gap junction elements were present (Fig. 4d). On the E face, this resulted in double and triple rows of tight junction particles alternating with faintly perceptible intervening gap junction pits. This pattern resembles the "special endothelial junctions" observed in systemic arteries and veins of the rat (Simionescu et al., 1976).

In nonmuscular arteries, the structure of endothelial junctions was as diverse as in the arteries of larger internal diameter. Gap junctions were present, although less numerous, within the meshwork of tight junctions (Fig. 5, a and b). The latter formed an interconnected network similar in appearance to that in the larger segments. In some regions, best seen on the E fracture face, the tight junctions formed two or more closely spaced parallel arrays of tight junction particles that alternated with intervening rows of gap junction pits (Fig. 5a). The appearance of these "special endothelial junctions" on both P and E faces, is best seen in Figure 5c. On the E face, the tight junction particles of uneven lengths stand out in sharp contrast to the faintly visible intervening rows of gap junction pits. Conversely, on the P face the gap junction particles form distinct rows separated by parallel spaces, the presumed site of the low tight junction ridges. As in the larger pulmonary segments, these profiles are similar to the "special endothelial junctions" observed in systemic arteries and veins (Simionescu et al., 1976).

Veins

Intercellular junctions between venous endothelial cells also were characterized by the presence of both tight junctions and gap junction elements. However, in contrast to arterial tight junctions, those of the venous side consisted of somewhat fewer parallel rows of particles (Table 2). They formed an interconnected network of particles of

Table 2 Characteristics of Replicas Examined by Freeze Fracture

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range in internal diameter (μm)</td>
<td>17-125</td>
</tr>
<tr>
<td>Number of endothelial junctions examined</td>
<td>52</td>
</tr>
<tr>
<td>Mean number and range of TJ elements*</td>
<td>4(2-6)</td>
</tr>
</tbody>
</table>

* The mean and range of tight junction elements was determined by counting the rows of tight junction particles/ridges at 0.25-μm intervals perpendicular to the longitudinal axis of the junctions.

Table 3 Number and Type of Junctions in Intra-acinar Arteries and Veins Examined by Freeze Fracture*

<table>
<thead>
<tr>
<th>Type of vessel</th>
<th>No of junctions examined</th>
<th>TJ</th>
<th>GJ</th>
<th>SEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>52</td>
<td>52</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Vein</td>
<td>61</td>
<td>61</td>
<td>23</td>
<td>5</td>
</tr>
</tbody>
</table>

* These figures were obtained as follows. Each replica of the area of contact between two endothelial cells was scored for the presence of tight junction and gap junction elements. Abbreviations: TJ = tight junction; GJ = gap junction; SEJ = special endothelial junction.
Figure 4  a: Intercellular junction from an artery measuring 42 μm in internal diameter. On the P face, TJ particles of varying length are situated in shallow grooves (arrowheads). On the P face, the TJ is a low ridge with few attached particles (arrow). Gap junctions (GJ) form tightly packed arrays of particles on the P face and complementary pits on the E face within the meshwork of the TJ. 75,000×. b: Intercellular junction from an artery, 62 μm in internal diameter. On the P face, GJ particles form both clusters (asterisk) and linear arrays (arrowheads). The latter usually run parallel to the tight junction ridges (arrows). Narrow apical furrows on tight junction ridges are indicated by short black lines. 70,000×. c: Intercellular junction from an artery, 62 μm in internal diameter. Gap junctions (GJ) are particularly extensive and the narrow apical furrows on the low P face ridges (arrows) are evident. 72,500×. d: Intercellular junction from an artery measuring 52 μm in internal diameter. In three sites on the E face, parallel rows of tight junction particles flank a central row of gap junction pits (arrows). In another area (arrowhead), three parallel rows of tight junction particles traverse through the midst of gap junction pits. Arrow head in right lower corner indicates direction of platinum shadowing. 76,000×.
FIGURE 5  Intercellular junctions from a nonmuscular artery measuring 23 μm in internal diameter. The replicas are of intercellular junctions obtained along the length of the same vessel. a: E face of an intercellular junction consisting of a network of 2-4 rows of TJ particles present in shallow grooves. Only a single GJ (asterisk) is present in this field. 62,500×. b: E face showing 4-7 rows of TJ particles. Pits of two GJ are seen on the lower right. In several areas (single arrows), rows of TJ particles run parallel and in close proximity. In one region (arrow head) a row of GJ pits is present between the TJ elements. 62,500×. c: A junctional complex showing the features of a "special endothelial junction." On the E face (area between the two black lines), closely spaced parallel TJ particles alternate with GJ pits. On the P face, parallel rows of GJ particles alternate with areas of presumed TJ ridges (arrow head). Aggregates of GJ particles (P face) or pits (E face) within the meshwork of the TJ are present above the "special endothelial junction" (asterisks). Arrow head in right lower corner indicates direction of platinum shadowing. 85,000×.

Various lengths (100-500Å) present in shallow grooves of the E face (Fig. 6b). On the P face the tight junctions formed low ridges with few associated particles, and in favorable replicas a narrow furrow could be discerned at the apex of the ridge (Fig. 6c). Gap junctions, while present within the meshwork of the tight junction elements, were smaller and less numerous than those between endothelial cells. Moreover, their size and number diminished even further in larger veins (compare Fig. 6, a, b, and c). As on the arterial side of the pulmonary circulation, in rare instances, tight and gap junction elements formed closely spaced alternating rows (Fig. 6d) which were similar to the "special endothelial junctions" described above.

Discussion

Previous freeze fracture studies of vessels in the systemic circulation have shown that, in arteries and veins (Simionescu et al., 1976), endothelial cell junctions have structural features that differ from those observed in arterioles, capillaries, and venules (Simionescu et al., 1975). In contrast to the systemic circulation, that of the lung has a number of unique characteristics. It is a low pressure system in which the capillaries are subjected to a variety of intraalveolar forces (Guyton et al., 1979), and are only sparsely supported by a delicate connective tissue meshwork (Weibel and Bachofen, 1979). Furthermore, evidence indicates that the endothelium of the lung plays an important part in metabolizing a variety of biologically active agents, including angiotensin I, bradykinin, serotonin, and norepinephrine, as well as in synthesizing and releasing a variety of prostaglandins (Fishman and Pietra, 1974). Finally, it has been suggested that endothelial cells in general, by virtue of being electrotonically coupled with each other and in close apposition with the underlying smooth muscle, may play...
Figure 6  a: P face of a junction in a vein measuring 34 μm in internal diameter. Patches and rows of GJ particles are interconnected by low TJ ridges with rare TJ particles attached (arrows). 74,000X. b: Junction in a vein measuring 190 μm in internal diameter. Shallow grooves containing TJ particles on the E face (arrow) merge with low P face ridges having few TJ particles (arrow). A few rare small GJ are present (arrow heads). 75,000X. c: Junction from a vein measuring 119 μm in internal diameter. The low P face ridges show few TJ particles and only a few small GJs are seen (arrows). 62,500X. d: A "special endothelial junction" present in a vein measuring 74 μm in internal diameter. Straight parallel rows of GJ particles alternate with presumed TJ ridges. In a few of the latter, some TJ particles are seen (arrows). Arrow head in right lower corner indicates direction of platinum shadowing. 112,000X.

a unique role in regulating vascular tone (Ryan et al., 1978).

Results from the present study show that in intra-acinar vessels of the lung the endothelial junctions of arteries have larger and more numerous gap junctions than those of veins. The presence of gap junctions strongly suggests, although in the absence of electrophysiological measurements does
not prove, that adjacent endothelial cells are electronically and/or metabolically coupled (Hertzberg et al., 1981). This has a number of implications for the lung. The coupling of endothelial cells through gap junctions to each other and their possible close contact through myoendothelial junctions (Ryan et al., 1978) with the underlying smooth muscle cells would facilitate a rapid and finely regulated response to vasoactive agents (Rose et al., 1977, Simpson et al., 1977, Lawrence et al., 1978). Indeed, that intact endothelial cells in a variety of arteries, including the pulmonary endothelium, play an integral part in the vascular response to vasoactive agents has recently been reported (Furchgott and Zawadzki, 1980). The metabolic coupling, facilitated by the presence of large numbers of gap junctions in arterial endothelium, would greatly enhance the efficacy of this interaction.

Physiological and functional differences notwithstanding, many of the morphological features of intercellular junctions in intra-acinar pulmonary vessels are similar to those described in systemic arteries and veins (Simionescu et al., 1976). These include: (1) larger and more numerous gap junctions in intra-acinar arteries than veins; (2) somewhat higher numbers of parallel rows of tight junction particles on the E face of intra-acinar arteries than veins; and (3) the presence of "special endothelial junctions" in both intra-acinar arteries and veins. The significance of the intimate association of alternating rows of tight and gap junction elements which comprise these "special endothelial junctions" is at present obscure. It does not, however, appear to be related to the prevailing intraluminal pressure, since they are found not only in both intra-acinar arteries and veins but also in systemic vessels (Simionescu et al., 1976) in which endothelial junctions are subjected to higher intraluminal pressures.

The tight junctions in all intra-acinar arteries examined had continuous, interconnected rows of junctional particles located mainly in grooves on the E face. In veins, the number of rows of particles was fewer, but continuous for the most part, suggesting that the quasi-discontinuous tight junctions observed previously in the venular segment of the pulmonary capillary bed are likely to be the most permeable portion of the pulmonary vascular bed (Schneeberger and Karnovsky, 1976). The appearance of venular as well as capillary tight junctions in the rat was similar to that reported in mouse lungs, thus confirming the earlier observations (Schneeberger and Karnovsky, 1976).

At present, little is known about the biochemical composition of tight junction elements or the physiological basis for their interaction with each other and with adjacent lipids of the cell membrane. Observations derived from freeze fracture studies suggest that probably there are compositional differences between the tight junction elements of endothelial cells, compared with those between epithelial cells. Epithelial tight junctions, fixation artefacts notwithstanding (Van Deurs and Luft, 1979), usually form continuous, smooth networks of fibrils which, in mammalian tissues, are found almost exclusively on the P face, leaving empty, complementary grooves on the E face (Schneeberger et al., 1978). Endothelial tight junction particles, by contrast, tend to preferentially partition, during freeze fracture, onto the E face where they are present in shallow grooves, leaving particle-poor ridges with a narrow apical furrow on the P face. Recent evidence indicates that the permeability of epithelial tight junctions is dependent on the presence of extracellular calcium (Martinez-Paloma et al., 1980) and in part on the presence of an intact, intracellular microfilament system (Meza et al., 1980). It remains to be determined what factors regulate the permeability of endothelial tight junctions.

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