was found to be ineffective. Higher concentrations of the drug were not used in this study because of its possible reversible arrhythmogenic action[6].

*Results and discussion.* Warming of the bathing medium from 21 °C to 36 °C for 2 min produced a decrease in contractility and an increase in the beating rate of ventricular strips. The strips did not show any disrhythmicity during a 30-min investigation period and the contraction amplitude reached the control level within this period. Nine out of 19 strips were then incubated with Ringer alone and 10 strips with Ringer containing iloprost (10 ng/ml) for 24 h at 4 °C. The strips were then superfused with Ringer alone under the same experimental conditions for a 30-min equilibration period and the test was repeated. Eight out of 9 strips which were incubated with Ringer alone showed apparent rhythm disturbances and a decrease in contractility following 2 min exposure to the warming (36 °C) of the bathing medium. The contraction amplitude was significantly less than that of the control during a 30 min investigation period (fig.). However, 10 strips which were incubated with Ringer containing iloprost for 24 h at 4 °C, did not develop rhythm disturbances to the warming stimulation, except one strip which was arrhythmic. The difference between the two groups was statistically significant when evaluated with Fisher's exact test[8] ($p < 0.01$). In this group the contractility did not differ from control measurements but was significantly higher than that observed with the strips incubated in Ringer alone ($p < 0.001$). Aconitine, when added to the superfusion medium at the concentration of 3.2 µg/ml, produced multifocal ectopic beats in strips preincubated in Ringer and Ringer containing iloprost. The contact time of aconitine with the strips was 1 min and was kept constant for all preparations. The onset of ectopic beats and of fibrillation in both conditions is summarized in the table. The calculated results obtained in both groups were significantly different when evaluated using the Mann-Whitney U-test[9] ($p < 0.01$). These results indicate that iloprost has a functional protective effect on the contractility and rhythmicity of frog ventricular strips in anoxic conditions, and support its beneficial effect on functional recovery in the isolated rat heart after 24 h hypothermic arrest[10]. Recent studies have been reported on the protective effects of $PGI_2$ and its stable analogs[4,5]. It has been suggested that the membrane stabilizing action of $PGI_2$ is the mechanism underlying its myocardial protective action. This speculation has further been supported by the decrease in 17-($^{131}$I)-heptadecanoic acid washout from ischemic myocardium in the presence of iloprost[11], a finding supporting the membrane stabilizing action of the compound. Whether or not the same mechanism is responsible for the functional protective effect of iloprost in frog myocardium remains to be elucidated. In addition, the dose-response relation of iloprost at concentrations ranging between 1 to 10 ng/ml should be studied in the winter season. Higher concentrations of the compound were not tested in the present study because of its reversible arrhythmogenic action observed in the guinea pig heart[6].

Onset of ectopic beats and of fibrillation in spontaneously beating ventricular strips preincubated with Ringer and Ringer containing iloprost (10 ng/ml) for 24 h at 4 °C. Arrhythmias were induced by aconitine added to the superfusion medium at the concentration of 3.2 µg/ml (mean ± SEM of 9 strips)

| | Onset of ectopic beats (sec) | Onset of fibrillation (sec) |
|---|---|---|
| In Ringer | 28.0 ± 4.1 | 72.0 ± 21.0 |
| In Ringer plus iloprost | 159.0 ± 44.0 | 260.0 ± 35.0 |

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## Telodendrial contacts between foveolar cone pedicles in the human retina

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*Summary.* The synaptic pedicles of foveolar cones in the human retina contact each other by means of telodendrial processes. Thus direct lateral coupling of photoreceptor terminals exists even in the area of highest acuity function.
*Key words.* Retina; human fovea; photoreceptors.

Interreceptor contacts have been demonstrated between synaptic terminals of photoreceptors in many vertebrate retinas[2,3]. Most contacts between cones and cones and between cones and rods are considered to be 'gap' junctions that may subserve electrical coupling[4]. Contacts between cones of primate retinas have been found between extrafoveal cones only[5,6] and not between cones of the central fovea. We here report from a light microscopical study the existence of direct contacts between neighboring foveolar cone pedicles of human retinas.

To minimize artifactual influences human foveas were obtained from eyes immediately after enucleation for melanomas. Only specimens in which the tumor was restricted to the anterior segment of the eye, not affecting macular vision, were used (Donors: two females, 72 and 82 years; 1 male, 47 years). 5 min. after enucleation the supramacular sclera was trephined and after short prefixing the underlying retino-choroidal disc was removed and immersed in the fixative (3% glutaraldehyde in a Sørensen phosphate buffer (0.1 M, pH 7.4)). Two specimens

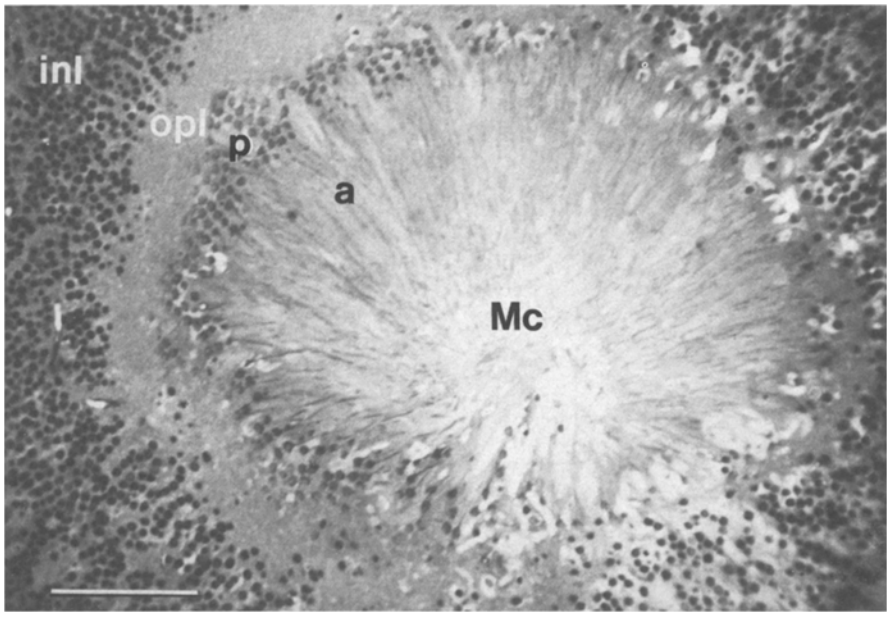


Figure 1. Tangential section of human fovea (0.7 µm, Stevenel's Blue). The central Müller fibers (Mc) of the foveal floor have a watery lightly stained cytoplasm while others ensheath the cone axons (a). Sectioning plane reveals first cone terminals in the ring of the pedicle layer (p). It is surrounded by the outer plexiform layer (opl) and inner nuclear layer (inl). Scale bar: 100 µm.

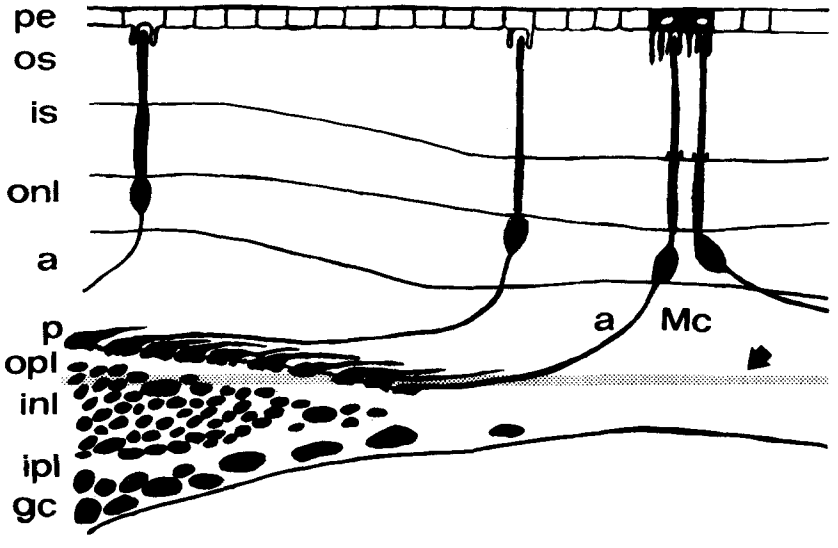


Figure 2. Schematic drawing of vertical section through central human fovea. Four cones are outlined to indicate the changing course and length of their axons. The changing thickness of the foveal retinal layers leads to oblique sectioning of central Müller cells (Mc), axons (a), pedicles (p), outer plexiform layer (opl) and inner nuclear layer (inl). pe: pigment epithelium, os, is: outer/inner segments, onl: outer nuclear layer, ipl: inner plexiform layer, gc: ganglion cells.

were postfixed in buffered 1% $OsO_4$. Following dehydration, blocks containing the fovea (circa 1 mm sidelength) were embedded in Epon. Serial semithin sectioning (0.7 µm) was performed in the horizontal plane beginning from the vitreous side of the retina. This allowed correction of sectioning plane before the photoreceptor layer was reached.

The foveolar cones are characterized by their slender elongated inner and outer segments and by the displacement of their pedicles[6] to the periphery via elongated axons (Henle fibers). This contributes to the characteristic foveal center where the proximal retinal layers are lacking. A specific type of Müller cells with lightly stained watery cytoplasm (Mc) constitutes the main element of the foveolar floor. The site of synaptic contact with second order neurons (outer plexiform layer) begins approximately 150 µm from the foveolar center. There the cone axon endings expand into cone pedicles (p in figs. 1 and 2) constituting a single layer in a concentric ring around the distal elements (perikarya, inner and outer segments) of the central foveal photoreceptors.

The outer plexiform layer (opl) is slightly bowed towards the pigment epithelium, a feature which in addition to the small vertical dimension of the pedicle layer allows only the exposure of a few pedicles within one section. The pedicles form a regular pattern, however (figs. 1 and 3a). This pattern probably reflects the mosaic of the foveolar cone inner segments and thus maintains the representation of spatial points projected on the retina. Axons and pedicles are separated from each other by prominent sheaths of Müller's radial fibers (Mf). The nuclei of these glial cells can be found i.a. directly between the pedicles. Most axons run in straight centrifugal directions, but some can be seen to deviate from the direction indicated by their distal portion and cross the route of others in a zone shortly before their pedicles. The axons insert obliquely and almost always medially into the pedicles (fig. 3a). The synaptic regions (s in fig. 3a) are somewhat shifted to the opposite side. Thin telodendria (d = circa 0.5 µm) can be seen to arise between these 2 poles and span the distances (up to 12 µm) towards a neighboring pedicle contacting its lateral surface (t, lt in fig. 3a). As indicated by median knob-like

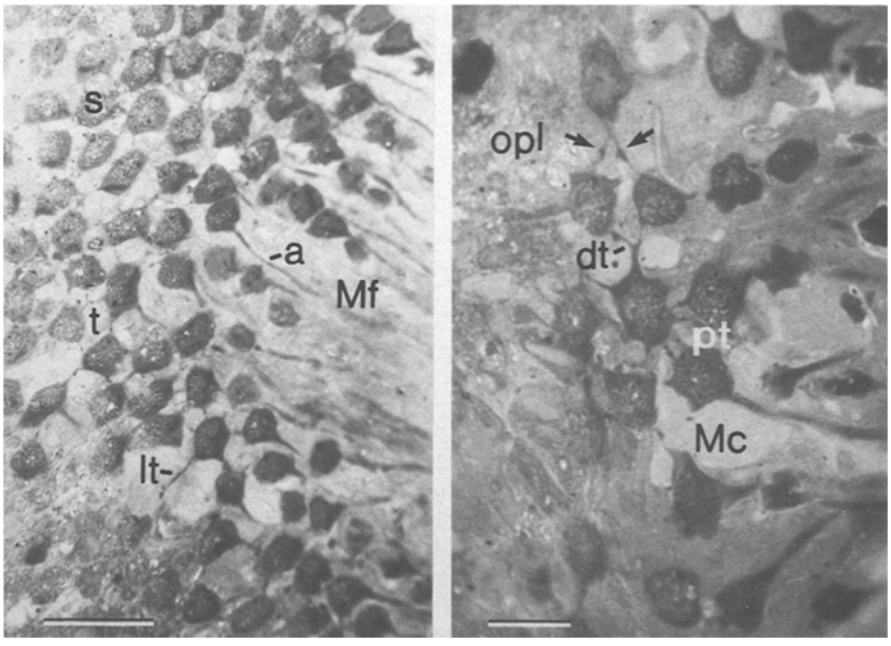


Figure 3. Semithin section of foveolar cone pedicles. a) Axons ensheathed by Müller fibers (Mf) radiate out to end in regular rows of pedicles with synaptic zones (s) facing the outer plexiform layer (opl). A network of telodendrial intercone contacts (t) crosses the glial space between the pedicles. The length of telodendria sometimes exceeds the diameter of the pedicles (lt). Scale Bar: 20 µm. b) Cone pedicles may be connected by pairs of telodendria (pt). Some telodendria appear to be connected medially between two pedicles (arrows), others are dividing (dt). Scale Bar: 10 µm.

thickenings (arrows in fig. 3a, b) both neighbors contribute to some of the connections. The occurrence of pairs of contacts indicates reciprocity in at least some cases. Most pedicles contact 6 other pedicles but some can also be observed to contact 7 neighbors. Some telodendria divide (dt in fig. 3b) and then each process contacts a separate neighbor.

With increasing eccentricity from this foveolar region the cone pedicles become more densely packed and the telodendria become smaller until they are obscured at the light microscopial level by the increasing number of rod spherules.

In the foveas of primate and human retinas the lateral displacement of cone terminals results in a single layered arrangement of pedicles having much larger diameters than the distal cell elements. This enables the cell mosaic to combine minimization at the input pole with multisynaptic complex wiring for processing of the information at the output pole in the outer plexiform layer. The present study provides evidence for contacts among the pedicles of human foveolar cones. Such contacts have not been observed in studies on primate foveas[5,6]. In the human fovea, contacts between perifoveolar human cone pedicles were reported in an early paper[8], but only one written report on the existence of connections within the central area of the human retina could be found[9].

Telodendrial contacts are considered to be gap junctions and sites of electrotonic coupling in mammalian retinas. These junctions are thought to serve in some way to improve the signal-to-noise ratio at the expense of signal acuity. Their reputed absence in the foveolar center of primate retinas was in agreement with hypotheses that spatial visual resolution closely parallels the diameters of single cones at their inner segments[10]. The present findings of inter-pedicle contacts indicate that they do not appear to interfere with maximum acuity functions. Their delicate dimensions and arrangement make it also unlikely that they have a prominent mechanical function, such as might be considered for the inner segment contacts[11,12]. Based on the nature of contacts between peripheral cones[6] and on the occurrence of features such as reciprocity and bifurcation we tend to attribute electrotonic coupling to these telodendria. However, this will have to be clarified in future electron microscopical studies. The vast majority ( > 90%) of the foveolar cones are green and red sensitive[13,14]. Therefore the existence of an extensive network of telodendria linking different spectral types presumably suggests coupling of the channels transmitting middle and long wavelength information already at the foveolar photoreceptor level. Thus the existence of this telodendrial network gives rise to a series of new questions concerning their role in visual functioning.

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