ing the city plays no role in the maximization of the downwind rainfall cannot be sustained. The maximum occurred downwind with sufficient frequency to be declared highly significant, if one uses the binomial test.

In the second statistical test, I evaluated the quadrant rainfall values in the 12 monthly wind-rain patterns by comparing the downwind values with those in the other quadrants. The differences, say, for downwind versus upwind, were ranked, and the one-sample Wilcoxon test was applied to these ranks. Addition of the negative ranks (upwind > downwind) for each comparison provided a number tested for its significance. The downwind versus upwind differences were significant at $P < .013$ (*10*). This comparison indicated that the downwind rainfall value differed greatly from those of the three other areas around St. Louis.

In the third test I used the ranks of the quadrant rainfall values in each summer month for each wind direction. For each of the 12 patterns, ranks were assigned with the maximum quadrant given rank 1 and the minimum given rank 4. These were summed to get a summer score for each quadrant. The downwind area rank score was 16, and tests of probability reveal it to be significant at $P < .0001$. None of the rank sums for the upwind, right, and left quadrants were statistically significant.

In this analysis of the summer rainfall around St. Louis, I have considered the possible urban effect by using the prerain winds to define the probable placement of an urban-induced rain maximum. The fact that 9 out of 12 possible monthly (three summer rain months and four basic wind directions) patterns and three out of four summer patterns had downwind maximums is strongly suggestive of an urban influence on precipitation over and beyond the city. Rotating the rain with the winds reveals a 22 percent rain increase in the area downwind of St. Louis.

Statistical tests dealing with both the placement of the highest quadrant rainfall and the positions of rainfall by quantity showed that the downwind values were significantly different and higher than those of surrounding areas. These results for prerain wind directions and rainfall distribution around St. Louis strongly support the concept that major urban areas lead to increased summer rainfall.

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11. I am indebted to C. F. Hsu for his assistance. This research was done under NSF grant ENV77-15375. The opinions, findings, and conclusions in this report are those of the author and do not necessarily reflect the views of the National Science Foundation.

18 January 1979; revised 9 March 1979

Permeability of the Cell-to-Cell Membrane Channels in Mammalian Cell Junction

Abstract. *The channels in the junctions of various mammalian cell types—primary cultures and lines— were probed with a series of linear fluorescent amino acid and peptide molecules of different size and charge. Permeability is limited by probe size and electronegativity, these two factors apparently being related reciprocally. In respect to both factors, mammalian junctional channels are more restrictive than insect channels; hence the mammalian channels are narrower, more polar, or both. The channels of the various mammalian cell types differed slightly from each other; in some types the serum of the culture medium affected the channel permeability.*

Cells of organized tissues and cultures commonly form junctions through which hydrophilic molecules are transmitted from cell to cell (*1-3*). The elements in this junctional transmission are specialized, leakproof membrane channels that link one cell interior to the other (*1, 3, 4*). They are the largest biomembrane channels known. A study of an insect cell junction, that of *Chironomus* salivary gland, showed that they transmit probe molecules—linear amino acids and peptides—up to 1800 daltons (*5*). The limit for transmission in mammalian cell junction—which is structurally quite different (*6*)—is not known. We show here that the limit is lower.

We studied the junctions of the following cultured cell types: primary rat liver (i) epithelioid and (ii) fibroblastic (*7*), (iii) calf lens epithelioid, (iv) rat liver epithelioid line RL (*8*), (v) rat fibroblast line B (*9*), (vi) human mammary fibroblasts (HUMF) (*8*), mouse fibroblast lines (vii) 3T3-42 and (viii) 3T3-BALB/c, and (ix) hamster fibroblast line BHK. For a comparison with cultured insect cells we used the fibroblast lines (x) AC-20 from the homopteran leafhopper *Agallia constricta* and (xi) ATC-10 from the dipteran *Aedes aegypti* (*10, 11*).

Junctional permeability was tested with the same series of fluorescent, linear probes (Table 1) used before on insect junction (*5*), but with the series augmented in the range 450 to 850 daltons. The molecules are of roughly constant abaxial dimension (14 to 16 Å, "width") and constitute a series of gradually increasing axial length. They are not degraded in cytoplasm (*5*), and their rates of loss are much less than their rates of transjunctional flux, in both the mammalian and insect cells (*12*). The 6-carboxyfluorescein supplements the series. This compound is more hydrophilic than fluorescein; like the labeled amino acids and peptides, it does not detectably permeate nonjunctional cell membrane from the outside (*13*). The probes were iontophoresed into the cells with the aid of a microelectrode, and their spread from the electrode through the injected cell and, transjunctionally, into the neighbors was continuously observed in a microscope dark field and photographed (*14*). To maximize sensitivity, we chose sparse cell groupings in which the injected cell was larger than the first-order neighbors, and made the fluorescence in the injected cell (roughly matched for all probes) much greater than the detection threshold. Permeability was scored positive when the tracer appeared in at least two neighbors, to make sure that it had not passed between incompletely divided daughter cells.

The outcome is summarized in Table 1. The feature that immediately stands out is the greater permselectivity of

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Table 1. Permeability of cell-cell channels. Cell-cell transfer is denoted on a scale (both visual and photographic) from ++++ (fluorescence of first-order neighbor approaching that of the injected cell) to + (first-order neighbor fluorescence just above detection threshold). A − denotes absence of detectable transfer and a ± denotes transfer just above threshold in <10 percent of first-order junctions tested. Each datum tabulated is the average of 25 to 133 first-order junctions tested (in most cases >35). The frequency of first-order junctions transferring the series of probes 1 to 8 in group I ranged from 47 to 94 percent, and those transferring probes 1 to 5 in group II ranged from 33 to 89 percent (except BHK probed with 5, which had a frequency of 10 percent). Frequencies for all probes in the insect cells AC-20 ranged from 53 to 100 percent, mostly >80 percent. A positive score required a minimum of two transferring junctions (see text). Permeability tests were performed on subconfluent cultures passaged [trypsin (0.5 g/liter) plus EDTA (0.2 g/liter), except primary cultures] 24 hours before the permeability tests. Lens cells, kindly provided by I. Fentiman, had been freshly obtained from calf lens and had been in culture for a few generations only. Abbreviations: LRB, lissamine rhodamine B; FITC, fluorescein isothiocyanate; Gly, glycine; Glu, glutamic acid; Tyr, tyrosine; Leu, leucine; and Pro, proline. The LRB is 152 daltons heavier than FITC, but LRB- and FITC-labeled probes have abaxial dimensions equal within 2 Å.

Probe	Molecular weight	Mammalian cells									Insect cells
		Group I		Group II							
					Primary						
		RL	B	Lens	Liver fibroblastic	Liver epithelioid	3T3-42	3T3-BALB/c	BHK	HUMF	AC-20
1 6-Carboxyfluorescein	376	++++	++++	++				+++	+++	++	++++
2 LRB SO_3H	559	++++	++++	+++	++++	++++	++	++++	++++	+++	++++
3 FITC(Gly)OH	464	++++	++++	+			++	+++	+	−	
4 LRB$(Gly)_6$OH	901	+++	+++	+++	+	++	++	++	++		
5 FITC(Glu)OH	536	+++	++++				+	++	+		
6 LRB(Glu)OH	688	++++	++++	++	+	++	+	++	−	−	++++
7 LRB$(Glu)_2$OH	817	+++	++	±	±	−	−	−	−	−	++++
8 FITC$(Glu)_2$OH	665	+	+				−	−	−		++++
9 FITC(Glu-Tyr-Glu)OH	851	−	−				−	−	−		++++
10 LRB$(Glu)_3$OH	946	−	+	−	−		−	−	−		++++
11 FITC$(Leu)_3(Glu)_2$OH	1004	−	−		−		−	−	−		++++
12 LRB$(Leu)_3(Glu)_2$OH	1158	−	−		−		−	−	−		++++
13 FITC$(Pro\text{-}Pro\text{-}Gly)_5$OH	1678	−	−				−	−	−		
14 LRB$(Pro\text{-}Pro\text{-}Gly)_5$OH	1830										++++

mammalian junction compared to insect junction: the FITC- or LRB-labeled molecules Glu-Tyr-Glu, $(Glu)_3$, $(Leu)_3(Glu)_2$, and $(Pro\text{-}Pro\text{-}Gly)_5$, ranging from 851 to 1830 daltons, which all pass through the *Chironomus* junction (*5*), did not pass detectably through any of the mammalian junctions. This disparity is not due to the channels in mammalian junctions being more susceptible to general blockade by action of these probes: when the mammalian junctions were probed with LRB$(Glu)_3$, FITC(Glu-Tyr-Glu), or FITC$(Leu)_3(Glu)_2$ simultaneously with (that is, in mixture with) the smaller 6-carboxyfluorescein or LRB SO_3H, the last two continued to pass (Fig. 1, I). The disparity is also not due to a difference in detection threshold or to culture as such: the junctions of the insect AC-20 cultures, which are similar in cell thickness (and overall size) to the cultured mammalian cells, behaved just like the junctions in the *Chironomus* organ (Table 1 and Fig. 1, II). A less complete set of tests on insect ATC-10 cultures confirmed this at least for the probes up to LRB Glu_3OH in the series (*15*). Evidently, the junctional channels of the mammalian cells are more restrictive than those of the three insect cell types.

In particular, the restrictiveness shows itself in the ability to sift charged molecules. The insect junctional channel shows no major discrimination between the probes with one, two, or three negative charges on their peptide backbone, in the range up to $(Glu)_2$; FITC$(Glu)_2$ and LRB$(Glu)_2$ with three charges, or LRB(Glu) with two charges, all go through the channel [in fact, at the resolution of the present method, there is no blockading charge discrimination by the insect channel even with molecules as large as $(Glu)_3$ (*5*)]. The mammalian channels do discriminate in this range. The channels of the B cell sieve out to

Table 2. Charge discrimination by channel. The permeability notation and scale are as described in Table 1. Abbreviations: MW, molecular weight; BC, backbone charges

Probe	MW	BC*	Permeability					
			Mammalian cells					Insect cells, AC-20
			Group I		Group II			
			RL	B	3T3-42	3T3-BALB/c	BHK	
LRB SO_3H	559	1	++++	++++	++	++++	++++	++++
FITC(Gly)OH	464	1	++++	++++	++	+++	+	
LRB$(Gly)_6$OH	901	1	+++	+++	++	++	++	
LRB$(Pro\text{-}Pro\text{-}Gly)_5$OH	1830	1						++++
FITC$(Pro\text{-}Pro\text{-}Gly)_5$OH	1678	1	−	−	−	−	−	
LRB(Glu)OH	688	2	++++	++++	+	++	−	++++
FITC(Glu)OH	536	2	+++	++++	+	++	+	
LRB$(Glu)_2$OH	817	3	+++	++	−	−	−	++++
FITC$(Glu)_2$OH	665	3	+	+	−	−	−	++++
LRB$(Leu)_3(Glu)_2$OH	1158	3	−	−	−	−	−	++++
FITC$(Leu)_3(Glu)_2$OH	1004	3	−	−	−	−	−	++++
FITC(Glu-Tyr-Glu)OH	851	3-4	−	−	−	−	−	++++
LRB$(Glu)_3$OH	946	4	−	+	−	−	−	++++

*Number of negative charges on the peptide backbone of the probes at cellular *p*H (7.4). The comparison is restricted to negatively charged molecules; our probe repertoire is insufficient for a comparison on the positive side. The FITC label has between one and two negative charges at cellular *p*H but, unlike the backbone charges, these are rather delocalized and hence local forces due to these charges should be correspondingly smaller.

some extent the $(Glu)_2$, notably the FITC$(Glu)_2$; and those of the two 3T3 cell types and the BHK cell sieve these molecules out completely and even sieve out the LRB(Glu) to some degree. This point is evident in Table 2, which summarizes the results, with the probes ordered by the number of backbone charges and, among probes of the same charge, by diminishing permeability. Apart from differences correlated with backbone charge, two other tendencies are seen. First, in probes with a particular backbone, an LRB label usually confers higher permeability than an FITC label. This may be a second-order effect of the delocalized negative charge on the FITC group. Second, with a given charge, the larger the backbone, the poorer is permeation. This probably reflects a steric effect.

This is the expected behavior of a channel guarded by a fixed charge or one in which hydrogen bonding limits permeation. Indeed, if we imagine the cell-to-cell channel to be made—like Singer's general channel model (*16*)—of protein subunits with polar amino acid residues lining an aqueous bore (*3, 17, 18*), some interaction with polar permeants would seem inevitable, particularly as the size of the permeant approaches channel diameter. Thus one is led to conclude that the mammalian channel is narrower or more polar than the insect channel and hence is more discriminating (*19*).

The mammalian cells differed in a small degree among themselves, falling roughly into two groups (Table 1). This is most readily seen if we attend to the tracer concentration in the first-order neighbors of the injected cell; this transjunctional fluorescence was generally strong in group I, comprising the RL and B cells, often as strong as in the injected cells, whereas in group II, comprising the other seven, except for LRB SO_3H, it was always weaker. Group II also generally displayed the more pronounced charge discrimination [compare, for example, the Glu and $(Glu)_2$ permeabilities of the two groups; Table 2].

The large difference in junction permeability between the mammalian and insect cells probably reflects a basic difference in channel structure. This brings to mind three major morphological differences: (i) the membrane particles of gap junction—the structures widely thought to contain the channels—in mammalian cells are smaller than those in insect and other arthropod cells (*18, 20, 21*); (ii) the insect cells have an additional junctional membrane differentiation, the septate junction, also made of organized particles, but absent in the mammalian cells (*6, 21*); and (iii), at least some of the mammalian cells here (*22*) have an additional differentiation of the tight (occludens) junction type (*23*), generally absent in insect cells (*6, 21*). There is also an important functional difference: insect cells do not couple electrically with mammalian cells in culture (*21*), whereas cells from different mammalian species couple with each other (*8, 24*), as do cells of different insect species from the same order (*21*).

The subtler difference between the two groups of mammalian cells may reflect a modulation of channel structure rather than a basic difference. The serum of the culture medium appears to be a factor here in at least some cell types. The permeability differences became blurred when the serum was removed. We experimented with two cell types from each group. Although they did not proliferate in serum-free medium, the cells kept well for at least 3 days. Within 2 days of serum deprivation, the number of 3T3-42 and BALB/c junctions transferring LRB(Glu) increased substantially and many transferred the formerly impermeant LRB$(Glu)_2$ (*25*). The permeation limit was then also lifted slightly

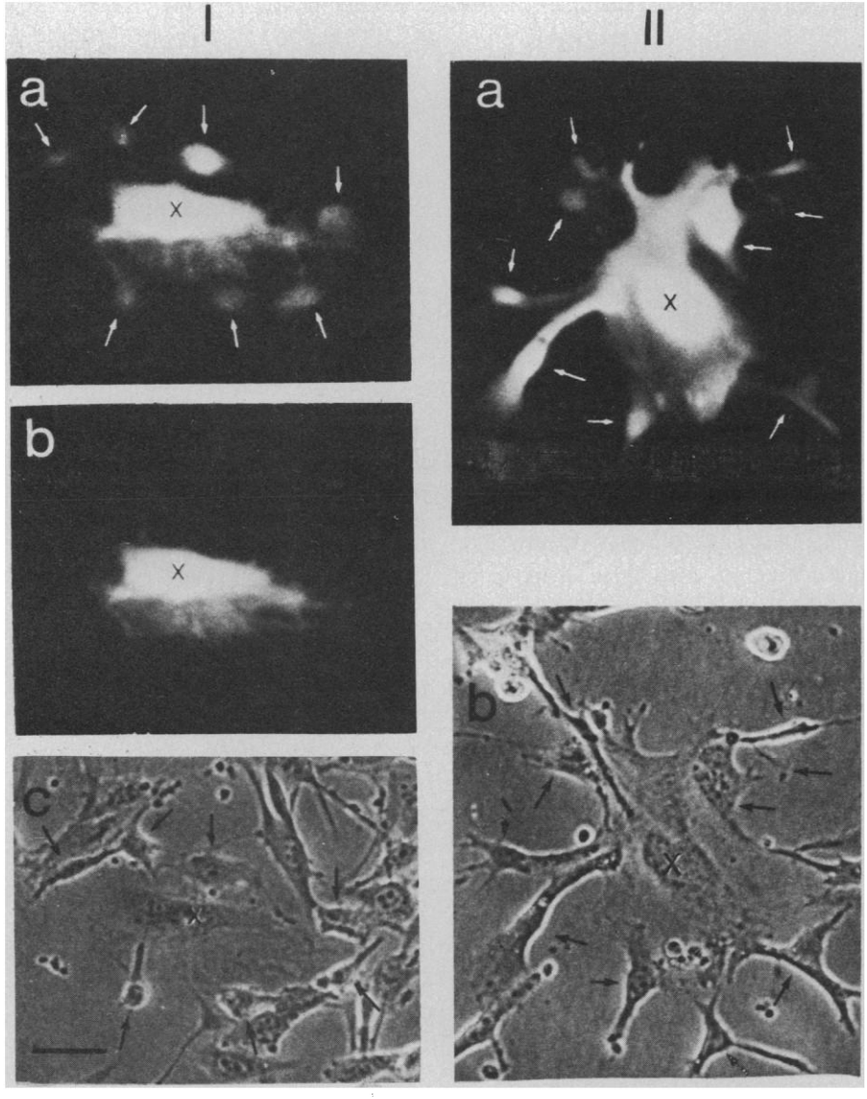

Fig. 1. Mammalian and insect cell junctions probed with fluorescent molecules. (I) A mixture of yellow-green fluorescent FITC(Gly-Tyr-Glu) (851 daltons) and red fluorescent LRB SO_3 (559 daltons) is microinjected (iontophoresis) into a mouse 3T3-BALB/c cell. The two molecular species are set apart by excitation and barrier filters. The injected cell (marked X) is the largest in the cluster. The dark-field photomicrographs show, in black and white, the distribution of the tracer fluorescence after the injection. (a) The smaller molecule spread to seven first-order neighbors (arrows) of the injected cell; (b) the larger molecule stayed within the confines of the injected cell. (c) The cell field is shown in phase-contrast after the injection. (II) The result of an injection of LRB$(Glu)_3$ (946 daltons) into an insect AC-20 cell (X) is shown for comparison (a). Here the injected molecule, even larger and more polar than the FITC(Gly-Tyr-Glu), spread to nine neighbors (arrows). [The one neighbor to which it did not spread (5 o'clock) is marked by a dotted arrow (b).] Scale bar, 50 μm for (I) and (II).

in B cells (but not in RL cells); the junctions became permeable to the LRB-$(Glu)_3$. The effect of serum removal in B cells had a latency of >24 hours and was completely reversible within about 24 hours of serum restoration.

One more result suggests that the channels of the two mammalian groups are not fundamentally different: when we cocultured them, the B made permeable junctions with the 3T3-BALB/c or with the lens cells. Whatever their difference, the protochannels from the membranes of the two groups still seem to pair.

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11. Growth (and test) media: Eagle-Dulbecco high-glucose (E-D) plus 10 percent fetal calf serum (FCS) for (i), (ii), (iv), and (v); E-D plus 10 percent calf serum (CS) for (vii) and (viii); BHK-2 plus 10 percent tryptose phosphate plus 10 percent CS for (ix); 199 plus 10 percent FCS for (iii); 199 plus 10 percent CS plus insulin (10 μg/ml) plus hydrocortisone (5 μg/ml) for (vi); and 199 plus Melnick's plus 2 m*M* glutamine plus 10 percent FCS for (x) and (xi). Explantation of (i) and (ii) in F-12 medium (1 day), then continued in growth medium. For coculture of (v) and (viii) we performed one experiment series with CS, another with FCS for 15 hours; heterologous junctions formed in both series.
12. The junctional transit times—the times between arrival of the probes at the injected cell boundaries and their detection in the first-order neighbors—generally ranged from 10 to 20 seconds; where junctional transfer was scored negative, observation times were at least 10 minutes. The half-times of fluorescence loss from isolated cells, recorded with a photodiode system, that images the cells through the microscope, were >30 minutes for all probes.
13. The amino acids and peptides were covalently labeled with lissamine rhodamine B (LRB) or fluorescein isothiocyanate (FITC) and purified (*5*). The 6-carboxyfluorescein (Eastman) had been introduced to biology for a different tracing function by J. N. Weinstein, S. Yoshikami, P. Henkart, R. Blumenthal, and W. A. Hagins [*Science* **195**, 489 (1977)]. We purified it by a procedure kindly communicated to us by W. Hagins; for a description, see S. J. Socolar and W. R. Loewenstein [in *Methods in Membrane Biology*, E. Korn, Ed. (Plenum, New York, 1979), vol. 10, p. 123]. Nonjunctional membrane impermeability was ascertained by bathing cultures for 0.5 hour in medium containing 5×10^{-4} *M* 6-carboxyfluorescein, FITC(Glu), LRB(Glu), $LRB(Glu)_2OH$, or $FITC(Glu)_2$ and then washing them: no fluorescence was visible in flat, well-attached cells, the only sort on which junctions were tested. "Rounded up" or loose cells, presumed to be dead or unhealthy, became fluorescent.
14. The probes were in aqueous solution (~1 m*M*) in the microelectrodes (tip, <5 μm). They were injected singly or, in some experiments (for instance, Fig. 1, I), in pairs: $LRB(Glu)_3$ and 6-carboxyfluorescein, FITC(Glu-Tyr-Glu) and LRB SO_3, $FITC(Leu)_3(Glu)_2$ and LRB SO_3. Iontophoretic currents ranged from 2.5×10^{-9} to 1×10^{-8} A.
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25. The frequency of permeable first-order junctions increased for LRB(Glu) from 16 to 71 percent in 3T3-42 (66 and 74 junctions tested before and after serum removal, respectively) and from 33 to 79 percent in BALB/c (90 and 135 junctions); for $LRB(Glu)_2$, from 0 to 19 percent in 3T3-42 (62 and 84 junctions) and from 0 to 36 percent in BALB/c (64 and 75 junctions); for $LRB(Glu)_3$, from 0 to 57 percent in B cells (180 junctions).
26. We thank Dr. I. Fentiman, A. McIntosh, and M. Stoker for cells; B. Rose and S. Socolar for advice and discussion; and J. Gray and C. Freites for construction of apparatus. J.F.-N. held postdoctoral fellowship 5F32 GM05802 from the National Institutes of Health. The work was supported by research grant CA14464 from the National Cancer Institute.

9 February 1979; revised 20 April 1979

Preferential Transmission of the Z Deficient Allele of α_1-Antitrypsin

Abstract. *The transmission of the Z deficient allele of α_1-antitrypsin was studied in 23 families, each with a single parent heterozygous for this allele. When the mother carried the Z allele, the distribution of phenotypes in the children did not differ significantly from the expected frequency. In contrast, when the father was the carrier, a significant increase of heterozygous phenotypes was observed in the children. This observation suggests that a selective advantage is associated with the expression of the Z allele in male gametes.*

α_1-Antitrypsin is the major inhibitor of protease activity in human serum (*1*). When analyzed by acid-starch gel electrophoresis, or, more recently, by isoelectric focusing, this inhibitor displays both microheterogeneity and polymorphism. The polymorphism is under genetic control, and the Pi (protease inhibitor) phenotype results from the expression of two autosomal codominant alleles in each individual (*2*). Some Pi alleles [I, P, S, W, Z, (−)] are associated with reduced serum concentrations of α_1-antitrypsin, ranging from 20 percent reduction for the I and S alleles, to 80 percent for the Z allele, and to complete absence for the "null" or (−) allele (*3*). Two major clinical disorders, pulmonary emphysema and liver diseases, have been shown to be associated with the Z allele, especially in homozygotes (*4*).

We have studied the transmission of the Z allele in 68 children from 23 families selected on the basis of the following criteria: (i) in each family, one parent had the phenotype M and the other MZ (*5*); (ii) each family included at least two children; and (iii) all the children in each family were available for investigation. The MZ parents were discovered either

Table 1. Transmission of the Z allele in children with one heterozygous parent.

Number of families	Number of children				
	Total	MM		MZ*	
		Girls	Boys	Girls	Boys
23	68	12	14	17	25

*Level of significance: $.1 > P > .05$.

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