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7. Supported by the American Cancer Society (P-363) and NSF (GB-1416). D.S.M. was a PHS trainee (T4-CA-5042). We thank Clarence Ellis for technical assistance, George Boxer for providing the actinomycin D, and T. J. McManus for performing the ATP assay.

8. Since this paper was submitted it has been reported that the addition of glucose reversed actinomycin D–induced inhibition of protein synthesis in ascites cells [G. R. Honig and M. Rabinovitz, *Science* **149**, 1504 (1965)]. The authors concluded that this effect was independent of RNA synthesis. Lack of data on energy metabolism of these ascites cells precludes a direct comparison with data in this report.

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Transport of Sugars and Amino Acids in the Intestine: Evidence for a Common Carrier

Abstract. D-*Galactose,* L-*arginine, and their respective actively transported analogs are partially competitive inhibitors of the active transport of neutral amino acids in the small intestine of hamsters. Since the aforesaid classes of compounds are all transported by similar, sodium-ion-dependent mechanisms and elicit countertransport of each other, all may share a common, polyfunctional carrier in which a series of separate binding sites, namely, one each for sugars, neutral amino acids, basic amino acids, and* Na^+ *are joined together, as in a mosaic.*

The small intestine can actively transport substances as different as sugars, amino acids, pyrimidines, and bile salts by similar, Na^+-dependent, stereospecific processes. In all cases, the net movement, including direction and extent, of the substrates into or out of the tissues is determined by the Na^+ gradient between the medium and the cells; that is, the process is freely reversible, and its net direction may be reversed by inverting the Na^+ gradient. Transport may require formation of ternary complexes of substrate, Na^+, and a membrane "carrier" (*1*). The carrier has not been identified, but it presumably is, or involves, protein (or proteins) with specific binding sites, and is "mobile"; that is, it is capable of providing access of bound, water-soluble substrates alternately to the extra- and intracellular fluids, across the lipidic barrier of the membrane (*2*). In principle, there should be at least as many different binding sites as there are classes of transported compounds and, consequently, as tacitly assumed by most workers, as many "carriers." However, recent work suggests an alternative hypothesis.

In 1926 Cori (*3*) suggested that sugars and amino acids may be absorbed "at the same place of the cell structure." Recently, reciprocal interactions between various Na^+-dependent transport mechanisms in the intestine have been noted. For instance, some sugars inhibit amino acid transport (*4, 5*), and some amino acids inhibit sugar transport (*6*). Also, although individual carrier systems have been postulated for the transport of different groups of amino acids, such as neutral, basic, acidic, and *N*-substituted (*7*), significant cross-inhibition between the different groups occurs (*8*). Some of the characteristics of the inhibition of transport of neutral amino acids by sugars and by basic amino acids are reported here.

Rings of everted hamster small intestine were incubated (*9*) with either C^{14}-cycloleucine (1-aminocyclopentane-1-carboxylic acid), which was assayed in trichloroacetic acid extracts of tissues and media with a liquid scintillation spectrometer, or with L-tyrosine, which was determined as phenol (*10*). Complete experimental procedures, including methods for demonstrating countertransport and for processing and presenting the data, have been described (*11*).

When the concentration of inhibitor (I) is constant and that of substrate (S) is varied, both D-galactose (Fig. 1) and L-arginine (not shown) competitively inhibit cycloleucine transport. In order to distinguish between fully competitive and partially competitive inhibition (*12*), the substrate concentration was kept constant and the inhibitor concentration was varied (Fig. 2). According to this method, both galactose and arginine behave as partially competitive inhibitors of cycloleucine transport, in contrast to the neutral amino acids—L-histidine, L-proline, and L-methionine—which behave as fully competitive inhibitors (*6*). From experiments of the first type (Fig. 1), kinetic constants for cycloleucine transport have been calculated. The average of six experiments gave the following constants, corrected for the extracellular space (*13*): K_m (the Michaelis constant, presumably identical with the dissociation constant of the substrate-carrier complex) was 5.15 mmole/liter (range: 3.8 to 6.0); and V_{max} (the maximum transport rate in conditions of saturation with substrate and with Na^+) was 2.74 μmole per milliliter of tissue water per minute (range: 2.2 to 2.9). These values and an average substrate concentration of 2.54 m*M* were used to calculate the theoretical curves shown in Fig. 2. Both curves *a* (Fig. 2) were calculated on the assumption of fully competitive inhibition (*12*, Eq. VIII.7) and a K_i (inhibition constant or dissociation constant of the inhibitor-carrier complex) of 14.5 mmole/liter. Curve *b* was calculated for partially competitive inhibition (*12*, Eq. VIII.28) and a K_i of 2.5 mmole/liter. Curve *b* fits the experimental data. Furthermore, when the ratio V_{max}/v (maximum rate/initial rate) is plotted against the inhibitor concentration (inset, Fig. 2), a parabolic curve rather than a straight line is obtained, as expected from the equations of partially competitive inhibition (*12, 14, 15*). A similar result was obtained with arginine as the inhibitor, whereas the neutral amino acids, L-histidine, L-proline, and L-methionine, acted as fully competitive inhibitors and gave straight lines.

If current enzyme kinetic theory is applied to the membrane carrier problem, a partially competitive inhibitor may be construed as a substance that binds to a site different from, but close to, the catalytic or substrate-binding site, so that a change in the apparent affinity of the catalytic site for its substrates, without a change in V_{max}, is induced. Such effects may properly be classified as "allosteric" (*12, 15, 16*) and operationally appear as a change in K_m to a higher, limiting value, K_m'. Partially competitive inhibition may be measured by the ratio K_m/K_m', which by definition is smaller than one (*17*).

From these considerations, two conclusions seem warranted. First, all the neutral amino acids studied (cycloleu-

cine, histidine, proline, and methionine) share a common binding site in the membrane, as should be expected. Second, if it is indeed true that galactose and arginine are allosteric inhibitors of the transport of neutral amino acids, it may be that three different substrate-binding sites (one each for sugars, neutral amino acids, and basic amino acids) plus the Na^+-binding site (*1*), are closely associated in the membrane, as in a mosaic, perhaps to form a macromolecular unit which we may tentatively identify with the "carrier." Such a conclusion is supported by the similarity of K_i for galactose (2.5 mmole/liter) determined above to K_m for galactose (2.2 mmole/liter) as calculated by Crane (*18*) from transport studies.

Furthermore, the capacity to inhibit transport of neutral amino acids is not restricted to galactose or arginine, but is shared by their respective, actively transported analogs. Among the basic amino acids, L-lysine is as effective as L-arginine, and L-ornithine is more so (Table 1). Among the sugars, and in agreement with other workers (*4*, *5*), galactose appears to be the strongest inhibitor, but other actively transported sugars, both metabolizable and non-metabolizable, are also inhibitory. Compounds not actively transported or, more precisely, having low affinity for the sugar carrier (*19*) are essentially inert, as may be seen by comparison of methyl-α-glucoside with its epimer at carbon No. 2, methyl-α-mannoside. Other nonactively transported sugars such as D-fructose, L-sorbose, and 2-deoxy-D-galactose were also not inhibitory (Table 1).

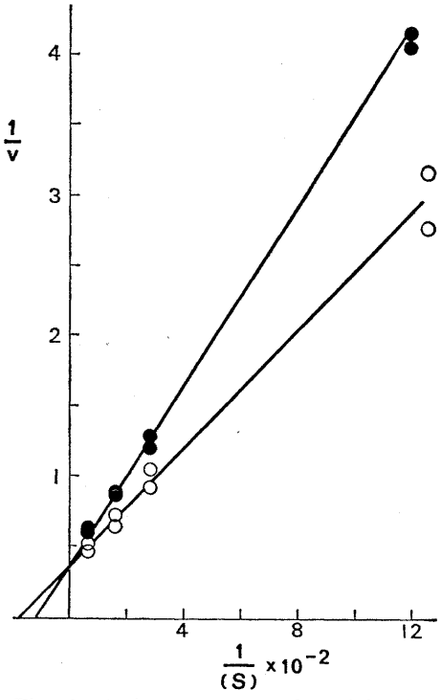

Fig. 1. Active transport of cycloleucine in the hamster intestine and inhibition by D-galactose. Rings of everted intestine were incubated (*9*) for 10 minutes in an oxygen atmosphere, in 4.5 ml of bicarbonate buffer (*26*), supplemented with a constant amount of C^{14}-cycloleucine and variable volumes of cold 0.3*M* cycloleucine; 0.3*M* mannitol was used to complete volumes to 5 ml. In one series (●), 0.25 ml of the mannitol was replaced with an equal volume of 0.3*M* galactose to give an initial galactose concentration of 15 m*M*. The initial concentrations of Na^+ and K^+ were 130 and 5.9 m*M*, respectively. The transport velocities (*v*, micromoles per milliliter of tissue water per minute), corrected for the extracellular space (*13*) and the average substrate concentrations ([*S*] = moles per liter of medium) are plotted as reciprocals (*27*). The straight lines have been calculated by the method of averages.

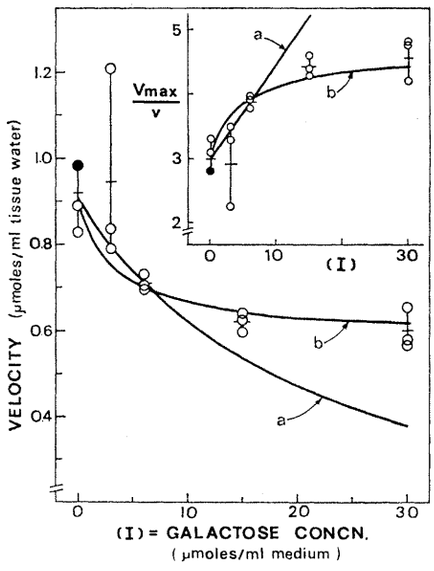

Fig. 2. Active transport of cycloleucine in the hamster intestine and inhibition by D-galactose. Incubations, 10 minutes in 4.5 ml of bicarbonate buffer supplemented with 0.3 ml of a 0.3*M* mixture of galactose and mannitol to give the galactose concentrations shown. The mixtures also contained a constant concentration of substrate: 2.7 m*M* C^{14}-cycloleucine. In the main body of figure, velocities are shown (*v*, micromoles of substrate per milliliter of tissue water per minute, corrected for the extracellular space, *13*). In the inset, the ratios of V_{max} to *v* are plotted. In both parts, the abscissa was the initial inhibitor concentration (*I*), that is, the galactose concentration (μmole/ml). Black circle indicates a double point. Other conditions as in Fig. 1.

As shown by Newey and Smyth (*4*), phlorizin was a poor inhibitor of amino acid transport, and its presence prevented the inhibitory effects of galactose (Table 1). Newey and Smyth (*4*) and Saunders and Isselbacher (*5*), both of

Table 1. Inhibition of the active transport of cycloleucine and L-tyrosine by sugars and amino acids. Rings of hamster intestine were incubated in oxygen atmosphere for 10 minutes in 4 to 5 ml of bicarbonate buffer with a ratio of Na^+ to K^+ of 22. In addition to the appropriate substrates, the media contained 0.5 ml of 0.3*M* solutions of the indicated inhibitors. Each set of figures represents a separate experiment in which substrate and inhibitor concentrations were kept constant. The initial concentrations ranged as follows (in micromoles per milliliter of medium); cycloleucine, 0.9 to 2.7; tyrosine, 2.2 to 3.2; inhibitors, 27.3 to 30; and phlorizin, 0.07 to 0.10. Percentage inhibitions were calculated in triplicate with respect to controls containing mannitol instead of inhibitor. A blank indicates that the compound was not tested.

Inhibitor	Percentage inhibition on transport of:	
	Cycloleucine	L-Tyrosine
L-Histidine	52 ± 1	38 ± 3
L-Proline	53 ± 1	
L-Arginine	11 ± 3	
D-Glucose		20 ± 3
6-Deoxy-D-glucose		22 ± 6
D-Galactose	34 ± 5	38 ± 5
L-Citrulline	72 ± 11	
L-Arginine	20 ± 6	5 ± 9
L-Lysine	20 ± 8	20 ± 7
L-Ornithine	34 ± 20	29 ± 10
D-Galactose		45 ± 1
Phlorizin	5 ± 3	0 ± 6
D-Glucose	21 ± 3	
D-Galactose	40 ± 2	28 ± 8
D-Galactose + phlorizin	13 ± 5	3 ± 6
Methyl-α-D-mannopyranoside	2 ± 10	0 ± 5
Methyl-α-D-glucopyranoside	26 ± 7	40 ± 5
Methly-β-D-glucopyranoside	19 ± 7	
1,5-Anhydro-D-glucitol		37 ± 3
D-Galactose	38 ± 2	53 ± 6
D-Melibiose	2 ± 5	
D-Glucose		12 ± 7
3-*O*-Methy-D-glucose	25 ± 10	20 ± 2
Methyl-α-D-glucopyranoside		28 ± 10
D-Allose	35 ± 3	
D-Galactose	52 ± 8	35 ± 9
D-Fructose	0 ± 5	0 ± 10
L-Sorbose		0 ± 5
D-Glucose	22 ± 7	
3-*O*-Methy-D-glucose	26 ± 6	
D-Galactose	46 ± 4	50 ± 5

whom used longer incubation periods (30 to 60 minutes), have suggested that galactose acts indirectly, either by competing with the amino acids for available energy supplies (*4*) or by giving rise to the "toxic" metabolite, galactose-1-phosphate (*5*): thus, phlorizin would act by blocking galactose entry into the cells. However, in the light of the foregoing results, it would appear that galactose acts directly at the membrane, and phlorizin may prevent its inhibitory effect on amino acid transport by virtue of displacing it from the sugar-binding site (*13*). The validity of this concept is supported by the short incubations used, together with the fact that nonmetabolizable sugars such as 6-deoxyglucose, 3-*O*-methylglucose and the methylglucosides (*20*) exert qualitatively identical effects as galactose.

As I see it, phlorizin itself is a poor inhibitor of amino acid transport because its sugar moiety is glucose, another poor inhibitor. To this may be added the possibility that the polyphenolic group of phlorizin may confer stability to the carrier. The reason galactose is the most effective inhibiting sugar remains unknown. Nevertheless, since it differs from glucose in having an axial $^{-}$OH group at carbon No. 4, it is plausible to invoke induction of conformational shifts among the associated binding sites, shifts that may be absent or less pronounced when the substituents are all equatorial (*21*). D-Allose, another substrate for the sugar carrier (*22*), also possesses an axial $^{-}$OH group and is also more strongly inhibitory than glucose (Table 1).

From Table 1 it also appears that the absolute effect of a given compound may vary considerably from one experiment to another. But the relative effects of different analogs are highly consistent, that is, sugars may be arranged in a series of increasing effectiveness as inhibitors of neutral amino acid transport, in a very reproducible manner. Such a series, applicable to both cycloleucine and L-tyrosine, may tentatively be defined as follows (in order of increasing effectiveness): methyl-α-D-mannopyranoside, D-glucose, 6-deoxy-D-glucose, 3-*O*-methyl-D-glucose, methyl-α-D-glucopyranoside, D-allose, D-galactose. The absolute variability encountered in these determinations may be related to the similar variability found while measuring kinetic constants for transport (*6*).

Finally, further evidence that these interactions occur at the membrane carrier rather than intracellularly is found in a study of substrate-induced countertransport (counterflow) which is, in theory, the best experimental way to demonstrate that two substrates share a common carrier (*2*). In these experiments, rings of intestine were allowed to accumulate substrate and then were transferred for a second incubation to fresh media containing 2,4-dinitrophenol, substrate, and another substrate which is called "elicitor." If the elicitor shares a common carrier with the substrate, the substrate flows from the tissues into the medium at a rate dependent upon the relative affinities of substrate and elicitor for the carrier, and upon their relative concentrations (*11*). The basic amino acid, L-arginine, and the substrates for sugar transport (galactose, glucose, methylglucosides) elicit countertransport of the neutral amino acid, L-tyrosine (*23*). Among the sugars, galactose is again more efficient than the methyl-α-glucoside, this in turn being more efficient than glucose (Table 2). Consistent with this pattern, other experiments show that amino acids also elicit counterflow of sugar transport substrates (*6*).

Current concepts of mobile carriers would virtually demand the conclusion that sugars, neutral amino acids, and basic amino acids, are transported in the small intestine of hamsters through a common carrier system which has separate binding sites for each of these groups of substances and for Na^{+}, but in which allosteric interactions between the associated binding sites occur. This proposal is consistent with current concepts of the "polyfunctional" nature of carriers (*24*) and seems to have the advantage of explaining in a unified and general way the activating effect of Na^{+} on a group of apparently different transport processes. At present, it seems that a common, polyfunctional carrier system, as suggested above, could most easily be understood in terms of the recently proposed concept of a "mobile membrane" (*25*). Here, the carrier is postulated to consist of binding site (or sites) fixed to one of the protein layers of the membrane: "mobility" would be conferred upon it as the result of local, transient engagements of the two protein layers that form the membrane.

Table 2. Amino acids and sugars as elicitors of L-tyrosine countertransport in the small intestine of hamsters. Rings of everted intestine were incubated for 15 minutes in 5 ml of bicarbonate buffer containing 2.5 m*M* L-tyrosine. At the end of this first incubation, L-tyrosine had accumulated as follows: 17.9 and 15.1 μmoles per milliliter of tissue water in experiments 1 and 2, respectively. Part of the tissues was then transferred for a 10-minute second incubation in mixtures of 5 ml of bicarbonate buffer plus 0.2 ml of 0.3*M* solutions of the indicated elicitors (*11*). These mixtures contained (initial concentrations, μmole/ml): 2,4-dinitrophenol, 0.19; L-tyrosine, 2.4, and elicitors, 11.5. The results are expressed as net changes in tissue tyrosine concentration, that is, as the difference in tissue tyrosine content between the first and second incubations: and as final percent fillings (FF). A positive net change in tissue tyrosine indicates influx; a negative sign, efflux; that is, substrate-induced counterflow (11). The results shown are the averages of triplicate determinations. Mannitol was used as a control.

Elicitor	Net change in tissue L-tyrosine (μmole/ml)	FF (%)
Experiment 1		
Mannitol	+ 0.30	700
L-Arginine	− 1.00	650
Methyl-β-D-glucopyranoside	− 4.40	500
L-Histidine	− 6.00	392
Experiment 2		
Mannitol	+ 0.60	655
D-Glucose	− 1.00	555
Methyl-α-D-glucopyranoside	− 3.40	445
D-Galactose	− 3.90	425

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17. Allosteric enzyme inhibition as well as activation may conform to the same equation (*12*, *15*), the difference depending on the

value of the $K_m/K_{m'}$ ratio, which is smaller than one in the first case and larger than one in the second. (For instance, in the experiment of Fig. 2, the $K_m/K_{m'}$ ratio was calculated as 0.56.) This suggests that it might be possible to interpret in the same manner the activating effect of Na^+ on sugar and amino acid transport and the reciprocal effects of sugars and amino acids already discussed.

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21. It appears that, for optimum interaction with the sugar carrier, sugars must possess a pyranose ring with as many substituent groups as possible in an equatorial position (*19*). Change of some of the groups to an axial position usually leads to a decrease in affinity. It seems possible that these changes in conformation of the sugars, although they still permit binding to the carrier, may induce on it the conformational shifts suggested in the text.
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Visually Evoked Potentials: Amplitude Changes with Age

Abstract. *Visually evoked potentials of 215 subjects, aged 1 month to 81 years, were studied. Amplitudes of waves in the first 250 milliseconds of the response changed markedly with age. In responses recorded from the occiput, there was a rapid increase in amplitude reaching a maximum in the 5- to 6-year-old group, with means of amplitudes at this age being about twice as large as means of some older age groups. With children 7 years and older there was a rapid decline in amplitude until ages 13 to 14, when an abrupt increase in amplitude appeared. Amplitude appeared to stabilize at about age 16. In older subjects, mean age 60 and beyond, significant changes were noted in the earlier components of the response.*

Shortly after his discovery of brain waves, Berger turned his attention to age differences in the electroencephalogram (EEG) and reported changes from infancy to adulthood (*1*). Others, notably Lindsley (*2*), Smith (*3*), Bernhard and Skoglund (*4*), and Henry (*5*) soon described changes in brain wave frequency and amplitude. Alpha frequency was found to increase steadily with age in a roughly exponential curve with its asymptote reached at 12 to 16 years. Amplitude, on the other hand, rapidly increased between the ages of 3 months and 3 years, then significantly decreased at the 4th year, probably because of final closing of the fontanels (*2*). After this there was a gradual decrement in amplitude until stabilization occurred in late childhood.

Recently, electronic computers have provided a means for the study of summed evoked potentials—electrical changes recorded from scalp, initiated by brief stimuli such as a click or a light pulse. These previously obscure cerebral electrical changes, when related to the time of a stimulus, emerge from the background brain "noise" and can be studied. Summed evoked potentials are receiving systematic attention in the adult (*6*), and in premature and full-term infants (*7*). Lacking, however, is a description of evoked potential changes in their relation to increasing age. If salient EEG changes occur during the formative years, leveling off at about 16, what changes might one expect in the evoked potential?

We now report on visually evoked potentials of 215 normal subjects, aged 1 month to 81 years, who were divided into 14 groups, with from 9 to 24 subjects in each group (Table 1).

The heads of subjects were measured and fitted with scalp electrodes that were then attached with bentonite paste. The electrodes were placed bilaterally, at O_1 and O_2 on the occiput and C_3 and C_4 in the central area, according to the "10–20" international system. The results from occipital leads only are reported here.

Ear-ground leads were used for reference. Each subject over 2 years of age reclined in a padded chair in a darkened room, with eyes open, facing a reflecting hemisphere 70 cm in diameter. Under 2 years, the subject sat on his mother's lap. The hemisphere was illuminated by a Grass PS-2B photostimulator lamp aimed at its center and positioned behind and to the left of the subject. The uniform flash that completely enveloped the subject's face, was of relatively low intensity (2 on the Grass PS intensity range of 1 to 16). The measured luminance of the hemisphere, 40 cm from the subject's eyes, was 2.2 millilamberts. One hundred flashes, 2 to 3 seconds apart, were delivered to each subject during a recording session. Every effort was made to insure comparable recording conditions. Attention was controlled by instructing the subject to fixate on a small black dot in the center of the hemisphere. As the recording sessions were short, generally 5 to 10 minutes, drowsiness was not a problem.

A Mnemotron computer of average transients was used to extract the cerebral responses to the flashes of light. These were plotted (by a Moseley X-Y Plotter) on paper (25 by 38 cm). The summed evoked responses from left occipital scalp were used for comparison and statistical evaluation. These responses (Fig. 1) were multiphasic with several recurring components in the first 250 msec of the response (*6*).

Three amplitude measures were made encompassing (i) 0 to 250 msec, (ii) 0 to 125 msec, and (iii) 126 to 250 msec of the evoked response of each subject. For each of the three time

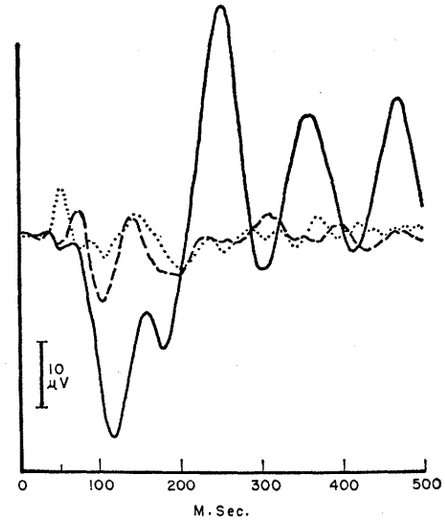

Fig. 1. Visually evoked potentials of three subjects of different ages. The high amplitude quality of the response during formative years and the potentiation of early components in later years are shown. A downward deflection indicates a positive change. Solid line, age 6; broken line, age 16; dotted line, age 60.