mine and the dopamine-induced increases in firing are not yet understood. However, it seems unlikely that the attenuation of GABA responses by dopamine involves a presynaptic action, such as an ability of dopamine to block release of GABA from striatonigral terminals impinging on reticulata neurons. Such an action would be expected to cause fixed increases in firing over the entire period of dopamine application, rather than the attenuations we observed during GABA pulses. A postsynaptic mechanism, such as a dopamine-mediated change in GABA receptor binding kinetics or in ion currents elicited by the interaction of the two transmitters at the membrane level, may provide a more likely explanation for the apparent modulation. The dopamine-induced increases in baseline firing, however, may reflect a direct excitatory action, a presynaptic action such as that described above, or a dopamine-mediated modulation of the effects of locally released GABA.

Further investigations will be required to ascertain the precise physiological relevance of the dopamine-mediated modulation. Endogenous release of dopamine by amphetamine also appears to diminish reticulata cell responses to iontophoretically applied GABA (*11*). It will be of interest to determine whether inhibition of reticulata neurons evoked by striatal stimulation, and presumably mediated by GABA, can be similarly attenuated by applied dopamine.

The monoamine neurotransmitters norepinephrine and serotonin have been assigned roles as neuromodulators (*12*), and we have now presented evidence for a modulatory function of dopamine. We have observed similar dopamine-induced attenuations of neuronal responses to GABA in the globus pallidus (*13*), the second output nucleus of the basal ganglia which has been reported to receive a sparse but widespread dopamine innervation from the SN (*14*). Demonstration of the interaction of GABA and dopamine in these two nuclei raises the possibility that dopamine may have a modulatory function in other areas of the central nervous system.

The nigrostriatal dopamine system has traditionally been viewed as influencing movement primarily by release of dopamine at postsynaptic sites within the striatum. Our results suggest that the net effect of dopamine on transmission of motor commands may reflect the combined actions of dopamine within the striatum and the SN. The ability of dopamine to act directly on basal ganglia output neurons to lessen their responses to GABA represents a means by which nigral dopamine neurons could influence transmission of movement-related messages without directly involving the striatum. Specifically, pars reticulata neurons constitute the link in the striatonigrothalamic pathway, both receiving striatal GABA inputs (*15*) and projecting heavily to the motor thalamus (*2*). Many cells included in these studies (55 percent of the cells exhibiting the modulatory interaction) could be antidromically activated from the VM thalamus. In addition, pars reticulata neurons give rise to major projections to other movement-related areas, including the superior colliculus and reticular formation (*2*). These results demonstrate, therefore, that dopamine, released from dendrites within the pars reticulata, could serve an important local function downstream from the striatum in adjusting or fine-tuning the relay of striatal commands to premotor nuclei outside the basal ganglia.

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22 July 1982; revised 28 September 1982

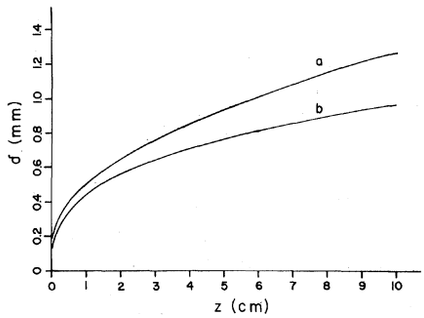
Diffusion Barrier in the Small Intestine

Smithson *et al.* (*1*) propose evidence for a diffusion barrier in the intestinal glycocalyx capable of impeding the transfer of low molecular weight nutrient precursors (disaccharides and short peptides) toward brush border enzyme sites. They are led to their conclusion in part by calculations of the thickness of "an unstirred layer." They consider the values obtained as "unphysiological" in that nearly half the intestinal volume would represent a zone of "intestinal fluid stasis." The authors propose an additional "important diffusion barrier" aside from aqueous diffusion zones, which presumably would justify shorter diffusion distances.

The authors' rejection of the unstirred layer thickness as unphysiological is based on an erroneous perception of what the thickness means and how it arises hydrodynamically. Analysis shows that for given values of the intestinal dimensions, stream flow rate, and substrate diffusivity, there exist a continuum of "unstirred layers" (more precisely, the diffusion boundary layer) commencing with nearly zero thickness at the stream entrance and growing as a function of the intestinal axis coordinate on passing to the distal end. Strictly speaking, the boundary layer reflects the ever decreasing radial concentration gradient of substrate along the axis coordinate. There is no macroscopic zone of fluid statis; fluid is convected in the axial direction including that containing the radial concentration gradients. For the laminar flow conditions in the experiments and in the case of complete diffusion control, the boundary layer approximation (*2, 3*) gives for the diffusion boundary layer:

$$\delta = 1.4693\left(\frac{DRz}{v_m}\right)^{1/3}$$

where D is the substrate diffusion coefficient, R is the radius (assuming a minimum cylinder), z is the axis coordinate, and v_m is the maximum stream velocity



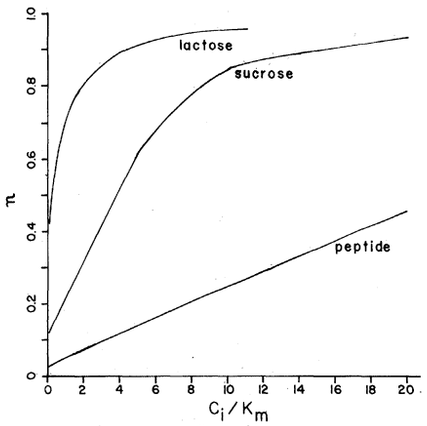


Fig. 1 (left). The diffusion boundary layer thickness, δ, as a function of position along the intestinal segment for sucrose. Curve a is derived from the exact solution to the convective-diffusion equations and curve b is the boundary layer approximation. The mean values are 0.76 mm and 0.64 mm, respectively. Fig. 2 (right). The effectiveness factor, η, as a function of C_i/K_m for the three substrates, where C_i is the concentration of substrate and K_m is the true Michaelis constant. The lactose reaction is far less diffusion-controlled than the other two.

(value on the axis). Fig. 1 shows this variation for the case of sucrose. It is possible, of course, to calculate a mean value of δ over the length of the intestine (z). Using the exact equations (*3*), I compute for sucrose 0.76 mm and for the peptide 0.74 mm. The results are nearly identical because D, R, z, and v_m are nearly the same for these substrates. They are also close to the results reported by Smithson *et al.* (*1*). However, average conditions do not prevail everywhere and, without some measure of the importance of deviations from the mean, the actual topography of the reaction is obscured. In fact, it is easily shown that 50 percent of the reaction occurs in the first 32 percent of the segment, where the boundary layer is less than the mean and substrate concentrations are highest. This relationship is consistent with current views of intestinal function.

A second point that must be treated is the extent to which each reaction is diffusion-controlled. Although the hydrolysis of sucrose and the peptide Gly-L-Leu-Gly-Gly are diffusion-controlled over much of the concentration range (*4*), diffusional effects on lactose hydrolysis are considerably less, owing largely to the twin effects of low V_m and high K_m. In spite of the fact that the mean boundary layer thickness for lactose hydrolysis is highest (1.4 mm) because of increased segment length and decreased flow rate, this reaction is less affected by diffusion. Fig. 2 shows the utilization factor, η, for each of the substrates (*4*). At concentrations equal to their true K_m values, the peptide has but 5 percent of the rate that would prevail were diffusion absent, and sucrose just 21 percent, but lactose is hydrolyzed at 71 percent of the theoretical maximum. At 2.5 K_m, its utilization factor is 84 percent. The reaction is only marginally affected by diffusion, hence it makes little sense to speak of a diffusion barrier for hydrolysis.

The mean boundary layer thicknesses presented do not constitute an unphysiological barrier to absorption. Indeed, it is a nutrient barrier in the glycocalyx that strikes one as unphysiological.

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4. The extent to which a reaction is diffusion-controlled is established by the value of the effectiveness or utilization factor, η, the ratio of the reaction rate in situ relative to that without diffusional effects. For Michaelis-Menten kinetics, it is a monotonic function of the Damköhler number. [See T. Kobayashi and K. J. Laidler, *Biotechnol. Bioeng.* **16**, 99 (1974).]
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30 April 1982

For many years, unstirred water layer models have dominated investigators' attempts to explain a perplexing "diffusion gap" that has been recognized in the kinetics of the small intestinal mucosa. In order to be credible, the notion requires that one reject the bowel's gross and microscopic anatomy and instead treat the bowel as a smooth surface. Nonetheless, as referenced in our report (*1*), in in vitro experiments unstirred water layer values for gut are three or four times that of other, anatomically smooth surfaces and are resistant to flow and stir rates up to the limits of the tissue's physical integrity. Further doubt on the importance of the unstirred water layer phenomena is cast by the results of in vivo studies that show the inability of the existing model to account for perturbations in the kinetics of hydrolysis of two disaccharides with similar physical properties, lactose and sucrose, and of an unrelated peptide, Gly-L-Leu-Gly-Gly (*1*).

DeSimone notes that two dissimilar substrates, sucrose and Gly-L-Leu-Gly-Gly, can be fitted to the existing model by considering the effects of axial flow. Lactose, identical to sucrose in many physical respects, could not be fitted. He argues that "[t]he [lactose] reaction is only marginally affected by diffusion," but he fails to explain why this knowledge should convince us of the importance of the unstirred layer.

The laminar flow equation that DeSimone presents predicts that the diffusion boundary in a gut of larger diameter should be proportionately increased. In fact, in perfused human gut, which has a cross-sectional area 50 times that of the rat gut, the value for the unstirred layer has been shown to be nearly the same (*2*).

The unstirred water layer model has yielded little of pathophysiological significance. Bacterial, parasitic, viral, inflammatory, and nutritional bowel maladies comprise a worldwide health problem. Since the dimensions of the bowel are generally unaffected by these disorders, surface phenomena related to the unstirred layer should be spared. In fact, malabsorption and maldigestion are rampant.

I maintain that the unstirred layer model has not fully explained the source of the known assimilation barrier. The properties of the boundary glycocalyx are offered as a possible alternative.

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