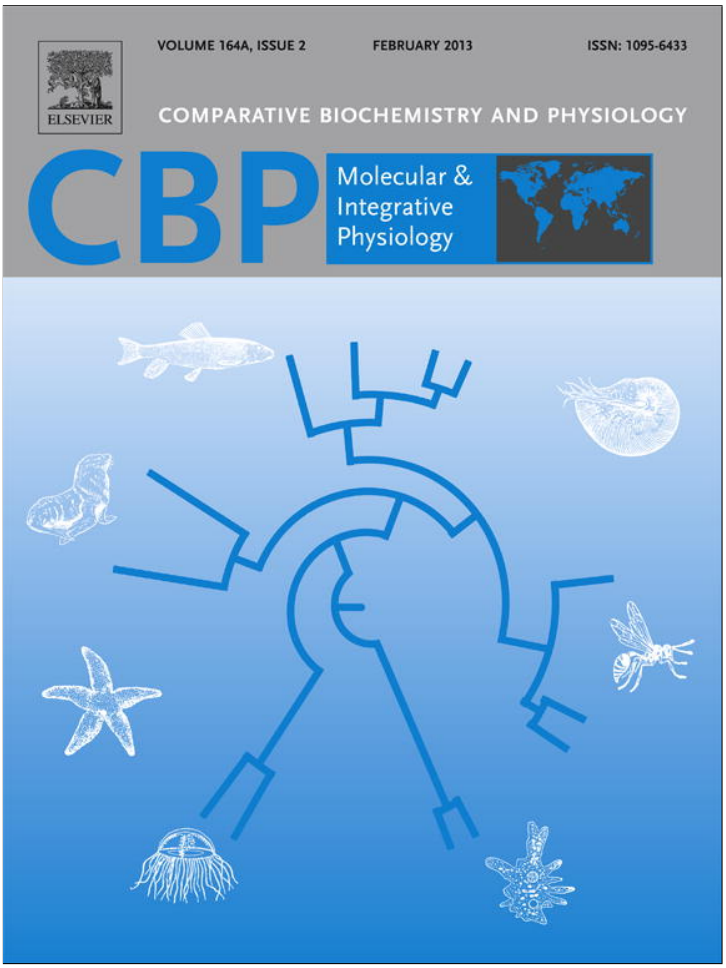

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Intestinal perfusion indicates high reliance on paracellular nutrient absorption in an insectivorous bat *Tadarida brasiliensis*

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ABSTRACT

Flying vertebrates have been hypothesized to have a high capacity for paracellular absorption of nutrients. This could be due to high permeability of the intestines to nutrient-sized molecules (i.e., in the size range of amino acids and glucose, MW 75–180 Da). We performed intestinal luminal perfusions of an insectivorous bat, *Tadarida brasiliensis*. Using radio-labeled molecules, we measured the uptake of two nutrients absorbed by paracellular and transporter-mediated mechanisms (L-proline, MW 115 Da, and D-glucose, MW 180 Da) and two carbohydrates that have no mediated transport (L-arabinose, MW 150 Da, and lactulose, MW 342 Da). Absorption of lactulose (0.61 ± 0.06 nmol min^{-1} cm^{-1}) was significantly lower than that of the smaller arabinose (1.09 ± 0.04 nmol min^{-1} cm^{-1}). Glucose absorption was significantly lower than that of proline at both nutrient concentrations (10 mM and 75 mM). Using the absorption of arabinose to estimate the portion of proline absorption that is paracellular, we calculated that $25.1 \pm 3.0\%$ to $66.2 \pm 7.8\%$ of proline absorption is not transporter-mediated (varying proline from 1 mM to 75 mM). These results confirm our predictions that 1) paracellular absorption is molecule size selective, 2) absorption of proline would be greater than glucose absorption in an insectivore, and 3) paracellular absorption represents a large fraction of total nutrient absorption in bats.

1. Introduction

Water-soluble nutrients (e.g., glucose and amino acids) are absorbed at the intestine via the transcellular and paracellular pathways. The transcellular pathway, in which there is transporter-mediated absorption of nutrients through enterocytes, is thought to be dominant in humans and many other mammals. The paracellular pathway, in which nutrients move passively through the tight junctions between enterocytes, might be thought to be of minimal importance so that the intestinal epithelium can be a better barrier to the absorption of small water-soluble toxins (Diamond, 1997; Karasov, 2011). Nonetheless, there are several species in which the paracellular pathway is an important, even dominant, route of absorption (Caviedes-Vidal et al., 2007; Caviedes-Vidal et al., 2008; McWhorter et al., 2010). In particular, small birds (Chang and Karasov, 2004; McWhorter et al., 2010) and some bats (Tracy et al., 2007; Caviedes-Vidal et al., 2008; Fasulo et al., 2012) have a high capacity for paracellular nutrient absorption. In experiments in which bats were orally dosed with nutrient-sized molecules (i.e., in the size range of amino acids and glucose, approximately MW 75–180 Da) that can only be absorbed paracellularly (e.g., rhamnose, MW 164 Da, or arabinose, MW 150 Da), 62–100% of the dose was absorbed. Absorption of arabinose and rhamnose is comparatively lower in non-flying mammals (Lavin et al., 2007; McWhorter and Karasov, 2007; Karasov et al., 2012). It should be noted that paracellular absorption in these and other species is size-selective; larger molecules (e.g. cellobiose, MW 342) have much lower absorption (Tracy et al., 2007; Caviedes-Vidal et al., 2008; Fasulo et al., 2012).

This variation among species with regard to the capacity for paracellular absorption could arise from several sources. Higher paracellular absorption of nutrients could be due to greater contact time with the intestinal epithelium (Lannernäs, 1995) or differences in gastric evacuation rates. High paracellular absorption could also be a result of differences in epithelial permeability, that is, bats may simply have "leakier" tight junctions than other mammals. Lavin et al. (2007) found that high absorption of paracellularly-absorbed probes was still evident in isolated duodenal loops of birds, indicating that there may indeed be differences among species with regard to epithelial permeability.

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To determine the epithelial permeability to nutrients in bats, we conducted luminal perfusions of the intestine in the insectivorous Brazilian free-tailed bat (*Tadarida brasiliensis*). These experiments represent the first measurements of amino acid absorption in a bat. We predicted that the size selectivity observed in vivo in mammals and birds for paracellular probes would be evident in our isolated intestinal preparations. Therefore, the absorption of arabinose (MW 150) should be greater than that of lactulose (MW 342). Because previous in vivo experiments demonstrated complete absorption of orally dosed arabinose in this species (Fasulo et al., 2012), we also predicted that paracellular absorption would represent a substantial fraction of nutrient uptake. Finally, because *T. brasiliensis* is an insectivore we predicted that glucose absorption would be relatively low compared to proline absorption (Diamond and Buddington, 1987; Karasov and Diamond, 1988).

2. Materials and methods

Adult Brazilian free-tailed bats (*T. brasiliensis*) were captured on the campus of Universidad Nacional de San Luis, San Luis, Argentina. We used bats on the same day of capture in order to minimize stress associated with keeping bats in captivity. Average mass was 15.66 ± 0.26 g and nearly all bats had visible abdominal adipose stores. All bats were adults and the great majority was female (6M, 29F). All animal procedures adhered to institutional animal use regulations and approved animal use protocols by the Animal Care and Use Committee of the Universidad Nacional de San Luis.

To examine tissue-level absorption, we used in situ intestinal luminal perfusions. In vitro methods such as everted sleeves, which may be ideal for measuring mediated uptake into enterocytes, are not suitable for measuring paracellular absorption because paracellular convective fluid flow is negligible (Pappenheimer, 1998) and blood flow is absent. Paracellular absorption is thought to rely on fluid absorption powered by osmotic gradients across tight junctions generated by Na^+-coupled concentrative transport of sugar and/or amino acids (Pappenheimer, 2001), and villus blood flow is probably essential for washing away absorbed solute and maintaining a high gradient for movement into capillaries (Pappenheimer and Michel, 2003).

For a given bat, we used one of three perfusates, which were designed to be isosmotic but vary in nutrient (proline and glucose) concentration, with the variation in nutrient concentration offset primarily with sodium chloride (Table 1). Both nutrients were set at 75 mM, 10 mM or 1 mM. For each perfusion, buffers were labeled with a tracer amount of [1-^{14}C]-L-arabinose and a tracer amount of [2,3-^{3}H]-L-proline, [methyl-^{3}H]-3-*O*-methyl-D-glucose (3OMD-glucose), or [galactose 6-^{3}H]-lactulose. We used radiolabeled 3OMD-glucose (a nonmetabolizable D-glucose analogue) rather than D-glucose to avoid complications associated with metabolism had we instead used radiolabeled D-glucose. We will address the implications of this methodological point in the discussion.

Table 1
Perfusion buffer components.

	Low nutrient (mM)	Mid nutrient (mM)	High nutrient (mM)
D-Glucose	1	10	75
L-Proline	1	10	75
L-Arabinose	1	1	1
Lactulose	0	1	0
$NaHPO_4$	1.2	1.2	1.2
NaCl	116	110	65
KCl	5	5	2.5
$MgSO_4$	1	1	1
$CaCl_2$	2	2	1
$NaHCO_3$	20	20	5

All buffers were pH 7.4.

Anesthesia was used throughout the surgery and perfusion (0.8 L/min oxygen flow, 3.5–4% isoflurane during surgical preparation, 1.5–2% isoflurane during perfusion). Anesthetized bats were taped to a heating pad (Deltaphase Isothermal Pad, Braintree Scientific Inc., Braintree, MA, USA) that maintained a constant 37 °C. Once on a surgical plane, the abdominal cavity was opened and the intestine was cannulated ~1 cm from the stomach using a rat gavage needle as the cannula, which was secured with suture. The mesenteric vasculature was maintained intact throughout all procedures. An exit cannula was placed distally, with an attempt to perfuse as much of the intestine as possible. The intestine was then flushed with prewarmed saline for 15 min to remove its contents, using a perfusion pump (1 mL min^{-1}). The saline was removed from the system and the experimental perfusion was started with a flow rate of 1 mL min^{-1}. Upon exiting the intestine, the perfusate returned to a reservoir and was continuously recirculated. The reservoir was kept in a water bath at 37 °C. The perfusion continued for approximately 2 h (117 ± 1.65 min) and then the perfusate was collected.

The perfusate was carefully weighed before and after the perfusion. Subsamples (50 μL) of the perfusate collected before and after the perfusion were counted using 5 mL Ultima Gold TM scintillation cocktail (Perkin Elmer) in 8 mL glass scintillation vials with a scintillation counter (Wallac 1409 DSA, Perkin Elmer). Immediately following the perfusion and euthanasia, the perfused section of intestine was removed from the abdomen and the length was measured using calipers. The intestine was then cut longitudinally and laid flat to measure circumference (we used the average of 3 measurements taken along the length of the perfused section). We calculated a 'nominal surface area perfused' (smooth bore tube) as the product of the length × circumference.

Absorption of each probe was calculated from the decrease in total radioactivity during the experiment, and was normalized by dividing by the duration (min) of the perfusion and either the length (cm) or nominal surface area (cm^2) of the perfused section of intestine. For arabinose and lactulose, we also calculated clearance, which accounts for slight changes in probe concentration over the course of the experiment. Clearance (μL min^{-1} cm^{-1} or μL min^{-1} cm^{-2}) was calculated by dividing absorption (calculated as above) by $[(C_{initial} - C_{final})/(C_{initial}/C_{final})]$, where C is the concentration (Sadowski and Meddings, 1993). Clearance values for glucose and proline were not calculated because they are absorbed by both carrier-mediated and non-mediated mechanisms.

To estimate the proportion of nutrient (glucose or proline) absorption that was paracellular, we used arabinose. Because its absorption is not carrier-mediated (Lavin et al., 2007), arabinose absorption rate is directly proportional to its luminal concentration. Thus, to calculate arabinose absorption at 10 mM, we multiplied arabinose absorption (which was measured at 1 mM) by 10. To then estimate the percent proline absorption that was paracellular, for example, we then divided this calculated arabinose absorption at 10 mM by the proline absorption measured at 10 mM and multiplied this fraction by 100%. We recognize that arabinose is not a perfect comparison molecule for proline because it has larger MW and is neutral rather than slightly nonpolar/hydrophobic like proline, but its use allows comparison to absorption measurements in intact animals of this species (Fasulo et al., 2012). In the Discussion we consider how differences between arabinose and the nutrients affect this estimate.

2.1. Statistics

We tested for differences between initial and final probe concentrations using paired t-tests. We used student's t-tests to detect significant differences between the absorption of glucose and proline. We used a paired t-test to detect differences in absorption and

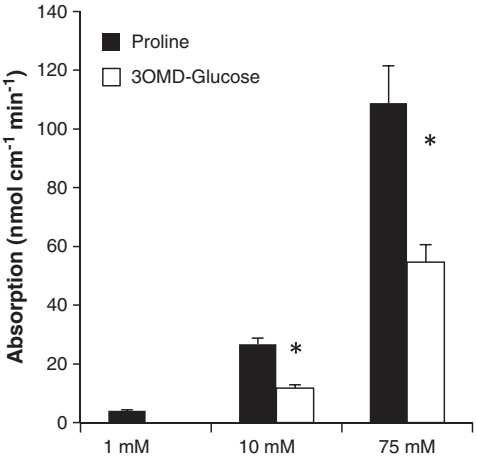

Fig. 1. Absorption of proline and 3OMD-glucose at 1, 10, and 75 mM in a 2 h intestinal luminal perfusion. Data are means ± SE. * indicates statistically significant differences between molecules at a given concentration. $N_{proline\ 1\ mM}=5$, $N_{proline\ 10\ mM}=9$, $N_{proline\ 75\ mM}=6$, $N_{3OMDglucose\ 10\ mM}=5$, $N_{3OMDglucose\ 75\ mM}=5$. Absorption of 3OMD-glucose was not measured at 1 mM.

clearance between lactulose and arabinose. Statistical significance was concluded when $P<0.05$. Values are presented as means ± SE.

3. Results

The concentration of proline in the perfusate changed over the course of the perfusion, particularly at low concentration. Proline concentration decreased from 1 mM to 0.74 mM ($P=0.002$), from 10 mM to 8.9 mM ($P<0.001$), and from 75 mM to 69.7 mM ($P=0.005$). 3OMD-glucose concentration did not change significantly at either 10 or 75 mM ($P>0.1$ for both). Arabinose ($P>0.3$) and lactulose ($P>0.1$) concentrations also did not change significantly.

Proline absorption was 4.1 ± 0.3 nmol min^{-1} cm^{-1} at 1 mM, 26.8 ± 2.1 nmol min^{-1} cm^{-1} at 10 mM, and 108.7 ± 12.8 nmol min^{-1} cm^{-1} at 75 mM (Fig. 1). Absorption of 3OMD-glucose was 11.7 ± 1.2 nmol min^{-1} cm^{-1} at 10 mM and 54.7 ± 5.9 nmol min^{-1} cm^{-1} at 75 mM. Absorption of proline significantly exceeded that of 3OMD-glucose at both 10 mM ($P<0.001$) and 75 mM ($P<0.01$). Calculated per nominal intestinal area, absorption of proline was 7.8 ± 0.5 nmol min^{-1} cm^{-2} at 1 mM, 44.4 ± 3.2 nmol min^{-1} cm^{-2} at 10 mM, and 198.3 ± 28.9 nmol min^{-1} cm^{-2} at 75 mM. Absorption of 3OMD-glucose per nominal intestinal area was 18.8 ± 1.2 nmol min^{-1} cm^{-2} at 10 mM and 95.7 ± 12.2 nmol min^{-1} cm^{-2} at 75 mM.

Arabinose absorption ($P<0.001$) and clearance ($P<0.001$) were significantly greater than that for lactulose (Table 2).

The percent of proline absorption that was paracellular was 25.1 ± 3.0% at 1 mM, 44.2 ± 2.1% at 10 mM, and 66.2 ± 7.8% at 75 mM (Fig. 2). The percent of 3OMD-glucose absorption that was paracellular was 109 ± 6.2% at 10 mM and 161 ± 14.3% at 75 mM.

To calculate an in vivo value for the apparent Michaelis constant (K_m^*) for proline transport, we generated an Eadie–Hofstee plot (Fig. 3). This K_m^* is 'apparent' because it is uncorrected for the unstirred

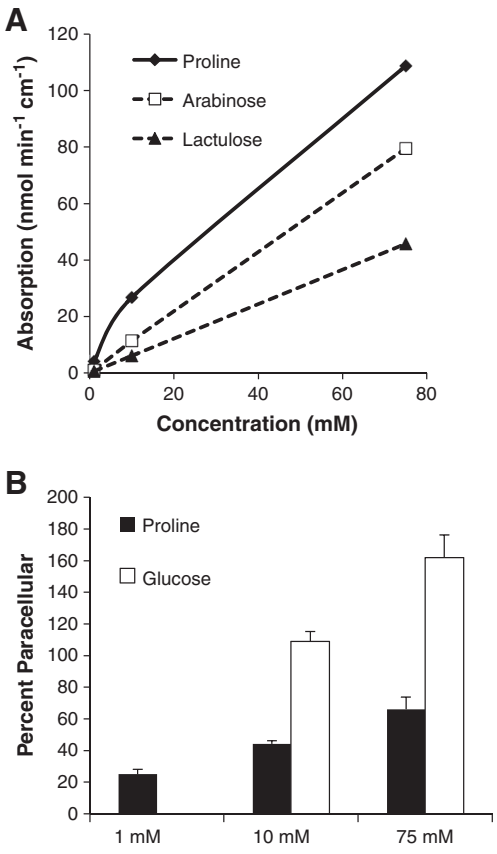

Fig. 2. A) Absorption of proline at 1, 10, and 75 mM and the absorptions of lactulose and arabinose calculated for the 3 concentrations. B) Apparent percent nutrient absorption that is paracellular based on absorption of arabinose. Data are means ± SE. Values for paracellular absorption exceed 100%, likely because of size differences between glucose (MW 180) and arabinose (MW 150; see Discussion). $N_{proline\ 1\ mM}=5$, $N_{proline\ 10\ mM}=9$, $N_{proline\ 75\ mM}=6$, $N_{3OMDglucose\ 10\ mM}=5$, $N_{3OMDglucose\ 75\ mM}=5$. Absorption of 3OMD-glucose was not measured at 1 mM.

layer effect (Karasov and Diamond, 1983) and because proline is transported by several transporters (Bröer, 2008). To isolate proline absorption that was transporter mediated, we first multiplied arabinose absorption by the concentration of proline, and then subtracted this from proline absorption. In the Eadie–Hofstee plot, the slope of the best fit line is $-K_m$. Thus, we calculate K_m^* to be 9.5 mM.

4. Discussion

We have conducted the first set of in situ intestinal perfusions on an insectivorous bat. As we predicted, (i) the absorption of passively absorbed molecules L-arabinose and lactulose was inversely related to molecule size, (ii) passive absorption could account for a large proportion of total uptake of both 3OMD-glucose and L-proline, and (iii) absorption of proline was relatively higher than that for 3OMD-glucose.

Table 2
Absorption and clearance of arabinose and lactulose.

		Absorption at 1 mM		Clearance	
	n	nmol min^{-1} cm^{-1}	nmol min^{-1} cm^{-2}	μl min^{-1} cm^{-1}	μl min^{-1} cm^{-2}
Arabinose	35	1.09 ± 0.04	1.91 ± 0.08	1.09 ± 0.04	1.91 ± 0.08
Lactulose	5	0.61 ± 0.06*	1.13 ± 0.18*	0.59 ± 0.06*	1.10 ± 0.18*

* Significantly different from arabinose, $P<0.001$.

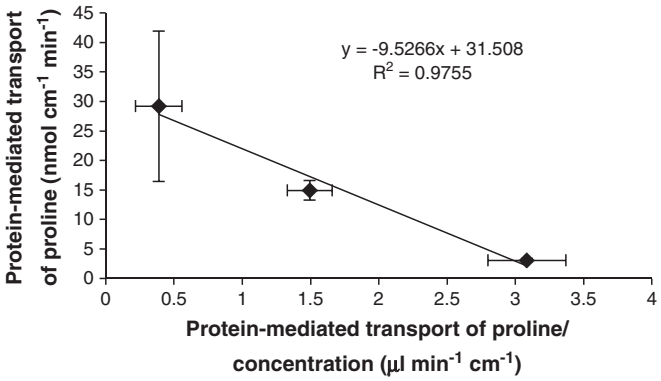

Fig. 3. Eadie–Hofstee plot for protein-mediated transport of proline. Protein-mediated absorption was calculated by subtracting concentration-corrected arabinose absorption from proline absorption. The apparent Michaelis constant (K_m^*) is the negative slope of the line, which was fit using a least squares regression.

We found that arabinose absorption was greater than that of lactulose, a finding that is in agreement with theoretical expectations for a sieving effect of the tight junctions and also in agreement with a vast amount of empirical data (Delahunty and Hollander, 1987; Elia et al., 1987; Bijlsma et al., 1995; Chediack et al., 2003; Lavin et al., 2007; Anderson and Van Itallie, 2009; Fasulo et al., 2012). In vivo data from birds, bats, and non-flying mammals indicate a size sieving function of the tight junction with a cutoff around a molecular radius of 4–6 Å, approximately corresponding to the size of lactulose (Chediack et al., 2003; Caviedes-Vidal et al., 2008; Anderson and Van Itallie, 2009). Presumably, this size sieving effect is a property related to the size of the tight junction channels. Molecules larger than 6 Å have very low but measurable paracellular absorption, which may result from discontinuities of the barrier (Anderson and Van Itallie, 2009). Our findings are also in agreement with the data of Lavin et al. (2007), who found molecular size-related differences in the clearance of paracellularly absorbed probes during intestinal perfusion experiments in rats and pigeons.

Estimation of the proportion of nutrient absorption that is paracellular is complicated by the size sieving effect. This is most notable when attempting to estimate the proportion of glucose absorption that is paracellular. When we use arabinose to estimate paracellular glucose absorption, we find the seemingly impossible result that more than 100% of glucose absorption is paracellular at both 10 and 75 mM. We ascribe this finding to the molecule size differences between arabinose (MW 150 Da) and 3OMD-glucose (MW 194 Da). The explanation may be that paracellular absorption is very high in the bat and that there is a large sieving effect of the tight junction, which slows the passive absorption of the larger 3OMD-glucose molecule more than it slows the smaller L-arabinose. In effect, the rapid paracellular absorption of arabinose, due to its smaller size, counterbalances the contribution of active transport to overall 3OMD-glucose absorption, especially if the active transport component is not particularly high (which it is not). It should be noted that a previous study of intact birds also demonstrated greater fractional arabinose absorption than 3OMD-glucose absorption (Karasov et al., 2012), suggesting that our finding is not an artifact of the surgical procedure. Also, it is worth noting that our tracer molecules have molecular weights up to 4 Da greater than their unlabeled counterparts, although it is unlikely that this substantially changes molecular radius, and therefore the sieving effect.

By similar considerations, the smaller size of proline (MW 115) relative to arabinose suggests that our estimate of the paracellular absorption of proline may be an underestimation. Also, proline is not as polar as arabinose, and relatively high paracellular absorption of water soluble molecules might be somewhat increased or decreased, depending on charge. However, in laboratory rats charge had relatively little effect on peptide fractional absorption (He et al., 1996). These kinds of experiments should be undertaken in bats.

Our estimate of the proportion of nutrient absorption that is paracellular may be somewhat high if mediated nutrient absorption is decreased by anesthesia (Uhing and Kimura, 1995; Uhing and Arango, 1997), although anesthesia may also reduce villus blood flow and thus decrease paracellular absorption too (Pappenheimer and Michel, 2003). However, the large proportion of nutrient absorption that we estimated was paracellular is in accordance with data from intact unanesthetized *T. brasiliensis*, which had essentially complete absorption of an orally gavaged arabinose dose, and in which more than 80% of glucose absorption was estimated to be paracellular (Fasulo et al., 2012). The other 2 bat species assessed to date (Tracy et al., 2007; Caviedes-Vidal et al., 2008) also have high (>60%) absorption of paracellularly-absorbed nutrient-sized probes, which greatly exceed similar measurements in non-flying mammals (McWhorter and Karasov, 2007; Karasov et al., 2012). Our study indicates that this difference between bats and non-flying mammals likely has its basis in species differences in permeability of the gut epithelium, although further in situ studies in other bats and non-flying mammals are necessary to confirm this. Interestingly, this greater permeability opens up the potential for greater backflow of nutrients from the circulation into the intestine, which is a finding made by Keegan et al. in their perfusion experiments with Egyptian fruit bats compared with laboratory rats (Keegan et al., 1979). However, the presence of mucosal glucose and amino acid transporters are presumably important for recovery of these nutrients, and they should be relatively effective when concentrations of nutrients are low in the lumen.

The value we calculated for K_m^* is at the upper range of values measured in other vertebrates using everted sleeves (4–9 mM; Karasov, 1988). Also, we used arabinose absorption to estimate the paracellular absorption of proline. Based on molecular weight, this leads to an underestimation (see discussion above), in which case our calculated K_m^* for in vivo mediated proline uptake would be somewhat overestimated. It is worth noting here again that proline is transported by several transporters and therefore the K_m^* we report reflects the affinity of the whole apical membrane of the enterocyte. We could not calculate a K_m^* for in vivo mediated glucose uptake because of the possibly larger error in estimating paracellular glucose absorption using the absorption of the smaller arabinose. In vertebrates generally, the K_m^* for glucose absorption ranges 0.6–6 mM (Karasov, 1988). Assuming that glucose absorption is the sum of a passive path and a single mediated path with a mid-range K_m^* of 5 mM, one calculates that the maximal mediated 3OMD-glucose absorption rate in our bats was 8.1 nmol min^{-1} cm^{-1}, and therefore, that the majority of 3OMD-glucose absorbed (54–86%) was absorbed passively.

We used a nonmetabolizable D-glucose analogue (radiolabeled 3OMD-glucose) instead of D-glucose to avoid complications associated with metabolism of D-glucose. But, we included unlabeled D-glucose in our perfusion solutions, begging the question how this might affect our conclusions. Affinities of both the brush border and basolateral glucose transporter(s) are lower for 3OMD-glucose than for D-glucose (Kimmich, 1981; Ikeda et al., 1989). Thus, at the highest glucose concentration, which was saturating for both D-glucose and 3OMD-glucose, our conclusions should hold. At lower concentration (e.g., 10 mM), the absorption of 3OMD-glucose likely underestimates the D-glucose absorption rate because of the former's lower affinity relative to the latter. Thus, at 10 mM we may have overestimated the proportion of absorption that was passive.

Protein dietary specialists (insectivores and carnivores) generally have particularly low glucose/proline uptake ratios when absorption of the two solutes is measured under near-saturating conditions

(i.e., 25–50 mM) (Diamond and Buddington, 1987; Karasov and Diamond, 1988). On average, vertebrate carnivores have a glucose/proline uptake ratio of ~0.4, while herbivores have an average ratio above 1, and omnivores are intermediate. In our perfusion setup, the ratio of total 3OMD-glucose absorption to total proline absorption was 0.44 and 0.50 at 10 and 75 mM, respectively. Thus our data are in accordance with the prediction that our insectivorous bat should have a relatively low glucose/proline uptake ratio.

5. Conclusions

In summary, these first intestinal perfusions in an insectivorous bat show that paracellular absorption accounts for a majority of total glucose absorption and confirm the results from intact individuals (Fasulo et al., 2012). Furthermore, a large portion of proline absorption is paracellular. Additionally, our data support our predictions that arabinose absorption should exceed that of lactulose, and that total proline absorption should be higher than glucose absorption. These results support the hypothesis that bats have higher paracellular absorption of nutrients than non-flying mammals, although future experiments in other bats and non-flying mammals should be conducted to confirm this.

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