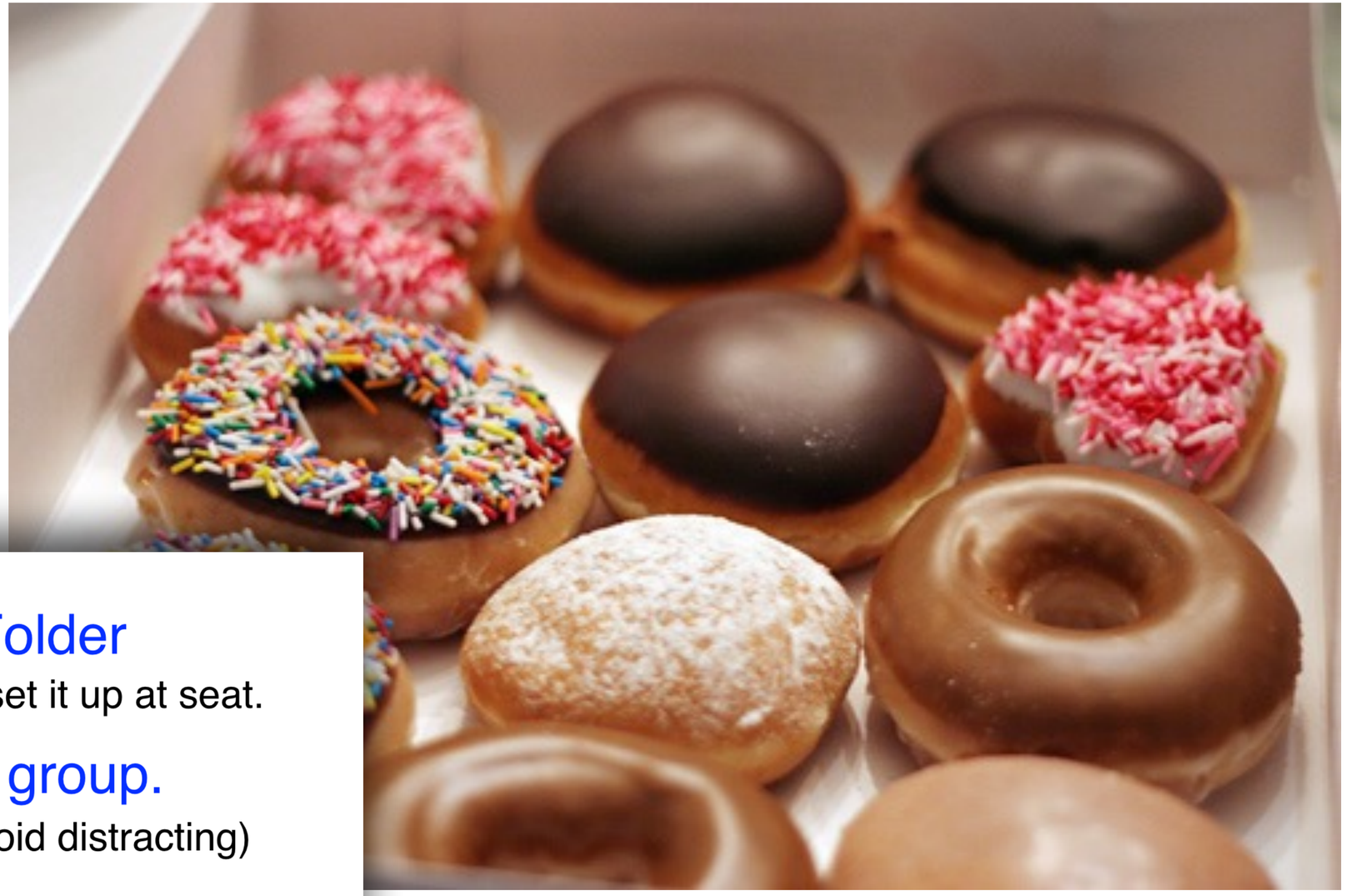


1. **Pick up** Name Folder

- Pick up name folder and set it up at seat.

2. **Sit** with your lab group.

- laptops almost closed (avoid distracting)

3. **Clicker** Attendance

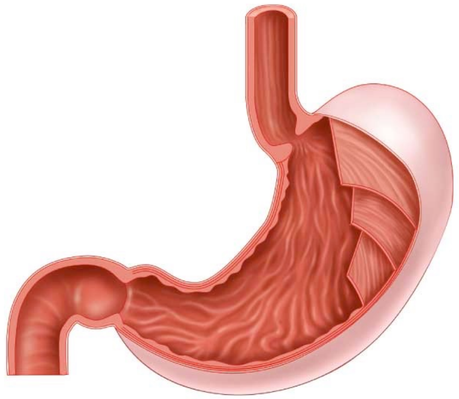
- Launch your Top Hat, and get ready to click.

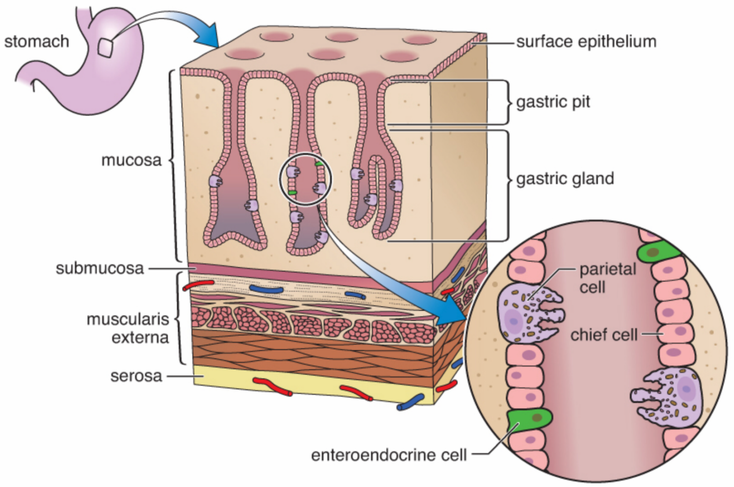
When does digestion begin?

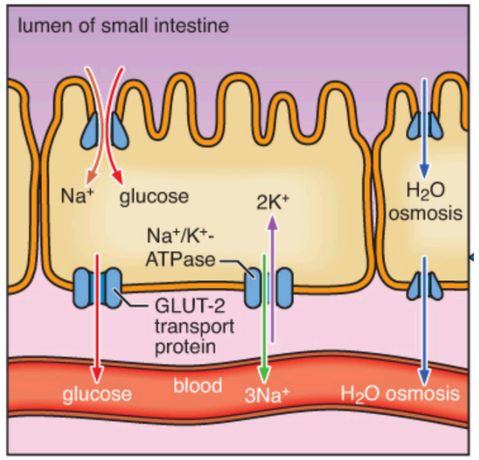
Digestion: Stomach

When you are eating, describe the process of digestion in the Stomach.

What **hormones** -> stimulate which **cells** -> to secrete what **enzymes/other** (or perform what **mechanical** actions) -> to digest what **food** molecules?







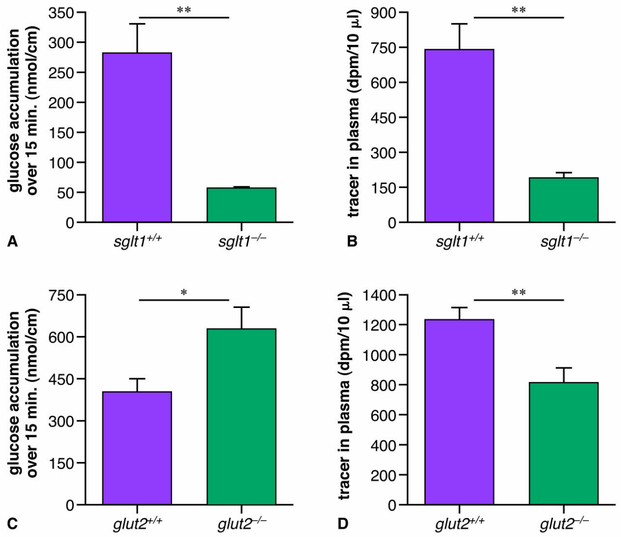
Prout
(Stomach)

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40
chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0

Muallem
(Parietal cell)

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038

Roder
(Absorption)



*The Origin of the Hydrochloric Acid in the Gastric Tubules.**

By Mabel Purefoy FitzGerald.

(Communicated by Prof. A. B. Macallum, F.R.S. Received June 4, 1910.)

(From the Biochemical Laboratory of the University of Toronto.)

[Plates 7—9.]

In 1823 William Prout† brought forward the view that the acid normally existing in the stomach was free hydrochloric acid, or to quote his own words, "free or, at least, unsaturated muriatic acid." This opinion was based on the analyses made by him of the gastric contents of the rabbit and of other animals, and of the fluid ejected from the human stomach in severe cases of dyspepsia. He said further: "With respect to the nature of this acid, very various opinions have been entertained. Some of the older chemists seem to have considered it as an acid *sui generis*; by others it was supposed to be the phosphoric, the acetic, the lactic, etc. No less various have been the opinions respecting its origin and use, some supposing that it is derived from the stomach itself, and is essential to the digestive process, others that it is derived from the food, or is a result of fermentation, etc.; in short, there seems to be no physiological subject so imperfectly understood, or concerning which there has been such a variety of opinions."

These words written in retrospection by the first exponent of the free hydrochloric acid theory, when read in the twentieth century, have the significance also of a prognostication, for during the past eighty-seven years interminable discussion has ensued between the advocates of the mineral and organic acid theories respectively, and in spite of the efforts of the physiologist, biologist, and bio-chemist in their several fields, uncertainty still exists on many and similar points. This is true in particular of the structure or structures of the gastric mucosa directly concerned with the formation and secretion of the hydrochloric acid, as well as of the existence even of hydrochloric acid in a demonstrable form within the gland tubules.

Article

The origin of the hydrochloric acid in the gastric tubules

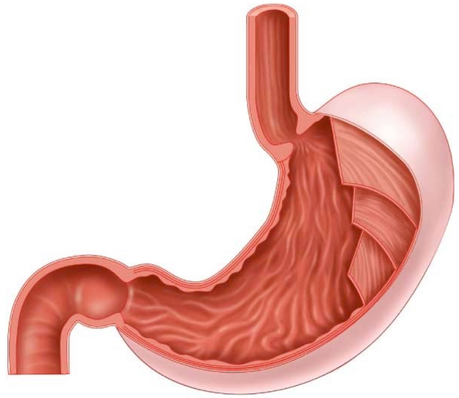
Mabel Purefoy Fitzgerald

Published: **26 November 1910** | https://doi.org/10.1098/rspb.1910.0067

Abstract

In 1823 William Prout brought forward the view that the acid normally existing in the stomach was free hydrochloric acid, or to quote his own words, "free or, at least, unsaturated muriatic acid." This opinion was based on the analyses made by him of the gastric contents of the rabbit and of other animals, and of the fluid ejected from the human stomach in severe cases of dyspepsia. He said further: "With respect to the nature of this acid, very various opinions have been entertained. Some of the older chemists seem to have considered it as an acid *sui generis*; by others it was supposed to be the phosphoric, the acetic, the lactic, etc. No less various have been the opinions respecting its origin and use, some supposing that it is derived from the stomach itself, and is essential to the digestive process, other that it is derived from the food, or is a result of fermentation, etc. ; in short, there seems to be no physiological subject so imperfectly understood, or concerning which there has been such a variety of opinions." These words written in retrospection by the first exponent of the free hydrochloric acid theory, when read in the twentieth century, have the significance also of a prognostication, for during the past eighty-seven years interminable discussion has ensued between the advocates of the mineral and organic acid theories respectively, and in spite of the efforts of the physiologist, biologist, and bio-chemist in their several fields, uncertainly still exists on many and similar points. This is true in particular of the structure or structures of the gastric mucosa directly concerned with the formation and secretion of the hydrochloric acid, as well as of the existence even of hydrochloric acid in a demonstrable form within the glad tubules.

Prout
(Stomach)



fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40
chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0

Trifecta!

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40
chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0

Explain these results

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71

Prout used silver nitrate to react with chloride salts to determine amount of chloride ion.

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40

Prout used a known amount of potassium hydroxide to exactly neutralize the solution, to determine free acid present.

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40
chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72

Prout added a large quantity of KOH, which neutralized all HCl to $KCl + H_2O$.

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
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total amount of chloride (g)	3.27	3.93	4.83

Total chloride is sum of 1st 3 fractions.

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
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chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72
total amount of chloride (g)	3.27	3.93	4.83

Total chloride is sum of 1st 3 fractions.

Numbers vary from rabbit to rabbit, but total amount of chloride is fairly consistent.

Table 23.1

From Prout, 1824.

Results from chloride analysis of stomach contents of three rabbits

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
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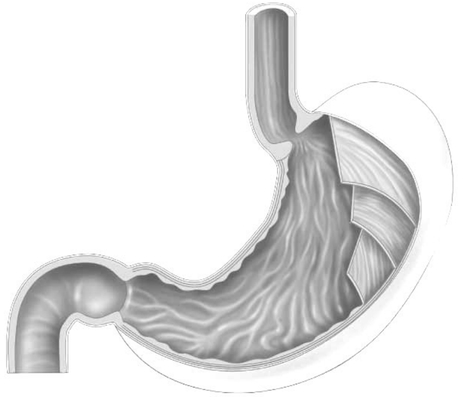
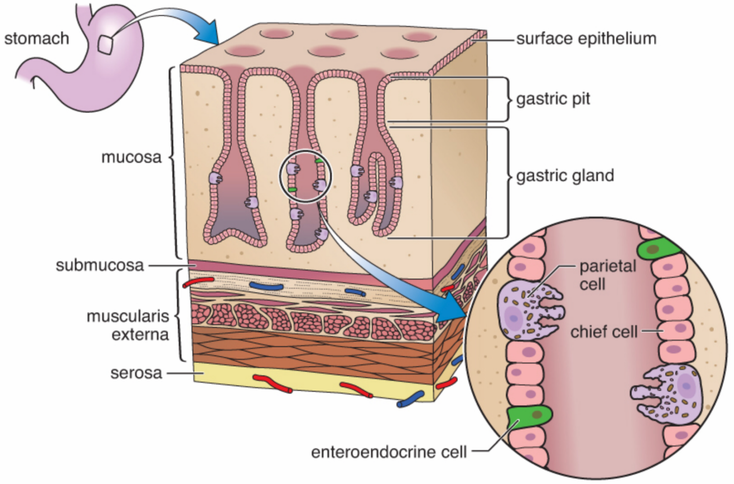
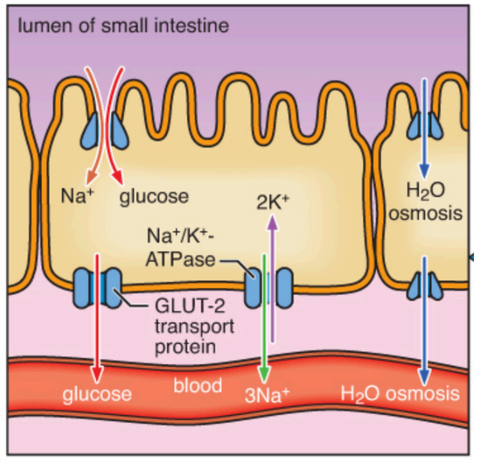
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0

Table 23.1

From Prout, 1824.







Prout
(Stomach)

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
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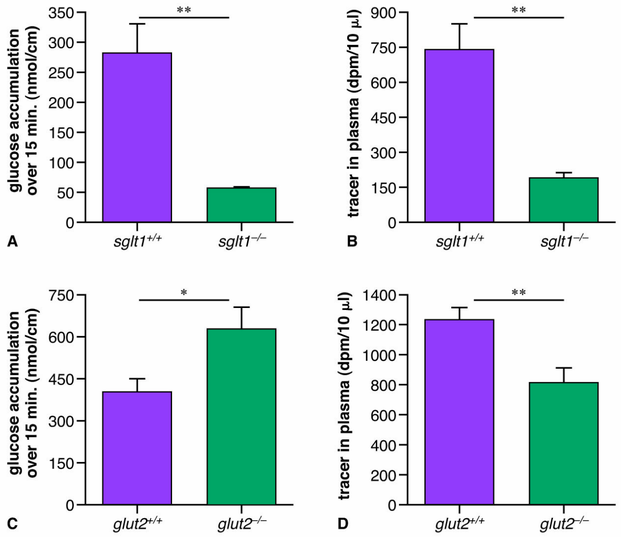
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0

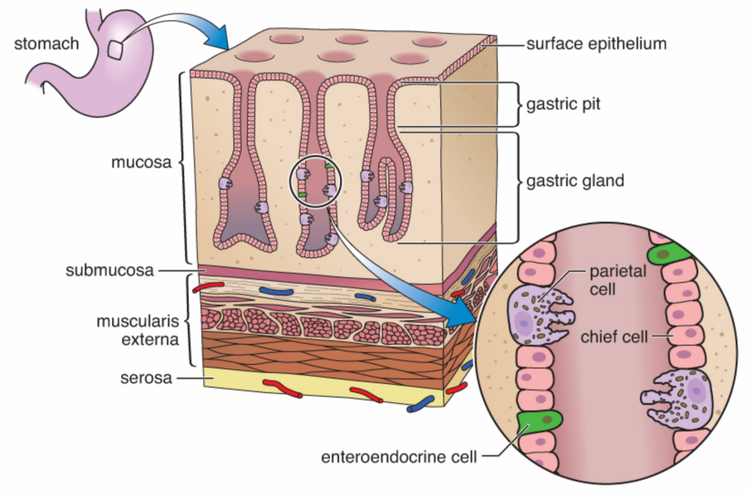
Muallem
(Parietal cell)

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038

Roder
(Absorption)



Muallem
(Parietal cell)



treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038

Muallem and colleagues performed a study to determine how stimulation of the parietal cells affected parietal cell internal pH. If pH of individual cells goes up, then you can conclude that hydrogen ions are being excreted from the cell and pH of the surrounding environment goes down. Although as you will see, there is a way to measure changes in pH inside and outside of the cells. *{Connections: Chloroplast pH is measured in a similar manner in Section 11.1.}* The scientists used a centrifugation technique to isolate parietal cells from the epithelium of the upper part of a rabbit's stomach. Keep in mind the structure of the parietal cell, especially the deep infolding on the lumen end of the cell, which increases the surface area for secretion.

The measurement of internal cell [redacted] as achieved through use of a dye that can permeate cells. This dye can be us[redacted]. The scientists measured the emission intensity of the dye at two differen[redacted]tensities is pH-dependent. Knowledge of the intensity ratio in solutions of known pH allows researchers to estimate intracellular pH. The scientists incubated cells with dye for 20 minutes and then washed the cells so that any dye not taken up by cells was washed away. Keep in mind that relatively small changes in pH, which is measured on a logarithmic scale, in single cell suspensions could actually lead to large decreases in pH in the stomach lumen.

Muallem and colleagues exposed cells to a medium that contained no sodium ions (Na^+) and found that intracellular pH went down (Table 23.2). When they added Na^+, the pH rapidly went up. Addition of a

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04

Trifecta

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038

Explain these results

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

DRAW a model parietal cell

To blood

Gastric pit
to stomach

DRAW a model parietal cell

To blood

Gastric pit
to stomach

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58

Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58

Sodium is required to
maintain pH homeostasis

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56

Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56

The major contribution to the rise in intracellular pH is activity of the Na^+/H^+ exchange protein.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0

Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0

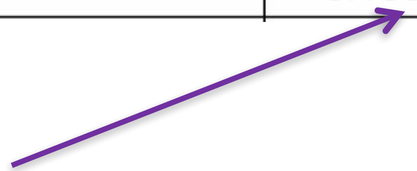
Shows that Na^+/H^+ exchange is important for maintaining intracellular pH in resting cell

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038



Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038

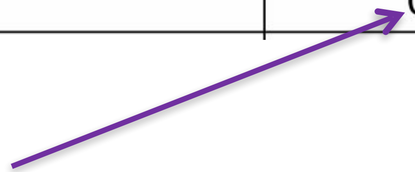
Histamine stimulates parietal cells to release acid, causing rise in intracellular pH.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04



Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04

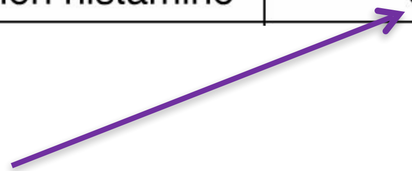
Histamine stimulates parietal cells to release acid, but requires sodium in extracellular medium.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04



Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04

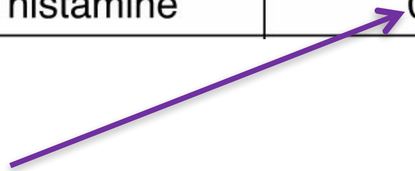
Absence of Na^+ and presence of Na^+/H^+ exchange inhibitor both have same effect of preventing release of H^+ from parietal cells

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01



Explain this result

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Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01

Histamine binds to a receptor: block the receptor and block parietal cell stimulation.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027

Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027

Parietal cell is stimulated.
Shows that histamine
increases cAMP.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027
histamine receptor antagonist, then histamine, then Na^+/H^+ exchange inhibitor, then chemical that increases cAMP	0.01

But if Na^+/H^+ exchange protein is blocked, increase in cAMP does nothing

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027
histamine receptor antagonist, then histamine, then Na^+/H^+ exchange inhibitor, then chemical that increases cAMP	0.01
H^+/K^+–ATPase inhibitor, then histamine	0.09
no Na^+, H^+/K^+–ATPase inhibitor, then histamine	0

Explain these results

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027
histamine receptor antagonist, then histamine, then Na^+/H^+ exchange inhibitor, then chemical that increases cAMP	0.01
H^+/K^+–ATPase inhibitor, then histamine	0.09
no Na^+, H^+/K^+–ATPase inhibitor, then histamine	0

H^+/K^+-ATPase responsible for further rise in pH to about 7.3

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then Na^+/H^+ exchange inhibitor, then chemical that increases cAMP	0.01
H^+/K^+–ATPase inhibitor, then histamine	0.09
no Na^+, H^+/K^+–ATPase inhibitor, then histamine	0
Na^+/H^+ exchange inhibitor added, then H^+/K^+–ATPase inhibitor, then histamine	0.02

Explain this result

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
[illegible] that increases cAMP	[illegible]
H^+/K^+–ATPase inhibitor, then histamine	0.09
no Na^+, H^+/K^+–ATPase inhibitor, then histamine	0
Na^+/H^+ exchange inhibitor added, then H^+/K^+–ATPase inhibitor, then histamine	0.02

If the cells were exposed to the Na^+/H^+ exchange inhibitor, there was no activation.

Table 23.2

Data from Muallem et al., 1988, text and Figures 2 to 8.

Intracellular pH changes from experiments on parietal cells

treatment	ΔpH
no Na^+	−0.58
Na^+ added after exposed to no Na^+	0.56
Na^+ and Na^+/H^+ exchange inhibitor added after exposed to no Na^+	0
histamine	0.130 ± 0.038
no Na^+, then histamine	0.04
Na^+/H^+ exchange inhibitor added, then histamine	0.04
histamine receptor antagonist, then histamine	0.01
histamine receptor antagonist, then histamine, then chemical that increases cAMP	0.125 ± 0.027
histamine receptor antagonist, then histamine, then Na^+/H^+ exchange inhibitor, then chemical that increases cAMP	0.01
H^+/K^+–ATPase inhibitor, then histamine	0.09
no Na^+, H^+/K^+–ATPase inhibitor, then histamine	0
Na^+/H^+ exchange inhibitor added, then H^+/K^+–ATPase inhibitor, then histamine	0.02

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Activation of the Na^+/H^+ and Cl^-/HCO_3^- Exchange by Stimulation of Acid Secretion in the Parietal Cell*

(Received for publication, November 9, 1987)

Shmuel Muallem‡§, Douglas Blissard¶§, Edward J. Cragoe, Jr.‖, and George Sachs¶§

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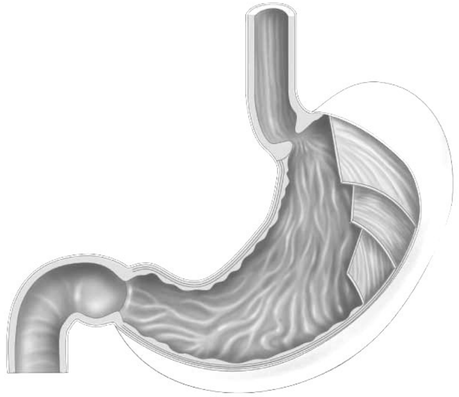
Upon stimulation, the gastric parietal cell secretes a large quantity of isotonic HCl across its apical membrane which must be accompanied by the generation of base in the cytosol. The ability of this cell type to regulate cytosolic pH (pH_i) was examined as a function of stimulation of acid secretion by histamine or forskolin. The pH_i was estimated from the change of fluorescence of the trapped dye, 2′,7′-bis(carboxyethyl)-5(6)-carboxyfluorescein-bis-carboxyethylcarboxy fluorescein in a purified cell suspension of rabbit parietal cells. Stimulation of the cell suspension raised pH_i by an average of 0.13 ± 0.038 pH units. The H^+,K^+-ATPase inhibitor, SCH28080 (2-methyl-8-[phenylmethoxy]-imidazo-(1,2)-pyridine-3-acetonitrile) had only a small effect on the increase of pH_i due to cell stimulation. The increase of pH_i, therefore, was largely independent of H^+,K^+-ATPase activity. In Na^+-free medium, where Na^+/H^+ exchange would be absent, the

across the apical membrane of the parietal cell.

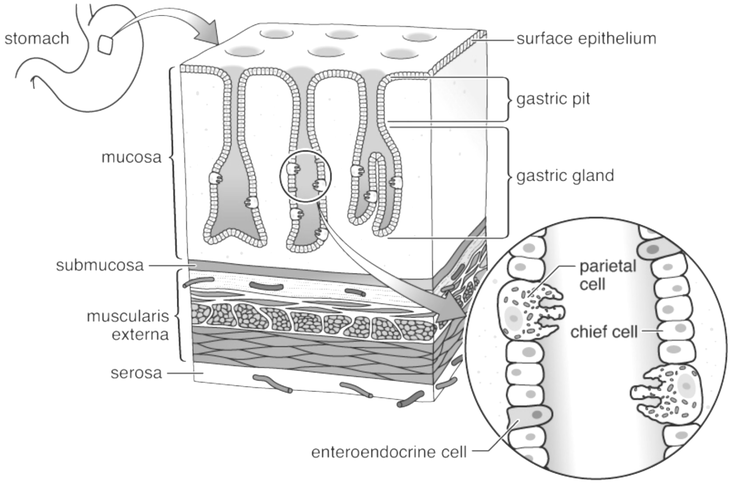
The regulation of cytosolic pH by cells usually requires the export of acid such as CO_2 or lactate that is generated metabolically or the extrusion of protons that enter the cell down their electrochemical gradient. An obligatory export of base is a less frequent situation.

The cell that is responsible for acid secretion in the stomach is the parietal cell. The transport enzyme that elaborates HCl is the HK-ATPase. In unstimulated cells, this enzyme is located in smooth-surfaced vesicular structures (tubulovesicles) in the cytoplasm. Upon stimulation, the HK-ATPase membranes move to the surface of the secretory canaliculus, forming microvilli. This canaliculus structure can be regarded as an inward extension of the apical membrane of the parietal cell. The secretion of protons is accompanied by an accumu-



Prout
(Stomach)

fraction of solution	rabbit 1	rabbit 2	rabbit 3
chloride salts (first fraction) (g)	0.12	0.95	1.71
exact amount of base to neutralize acid (second fraction) (g)	1.56	0.76	0.40
chloride salts after neutralization (third fraction) (g)	1.59	2.22	2.72
total amount of chloride (g)	3.27	3.93	4.83
other acids (fourth fraction)	0	0	0



Muallem
(Parietal cell)

treatment	ΔpH
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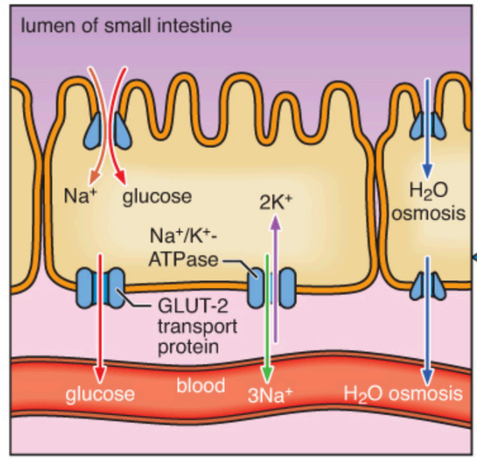
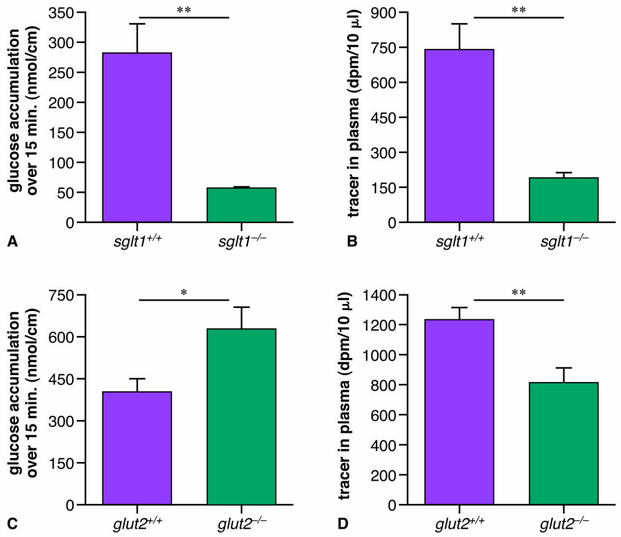


Roder
(Absorption)



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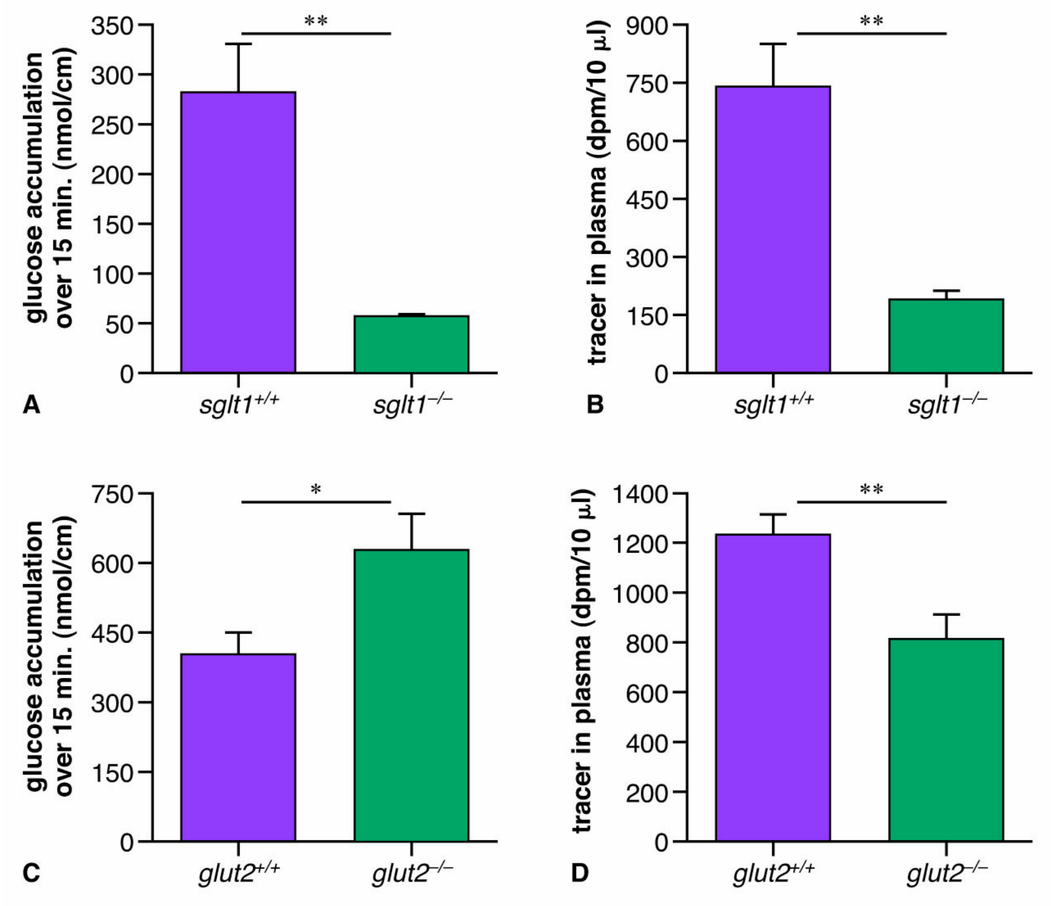
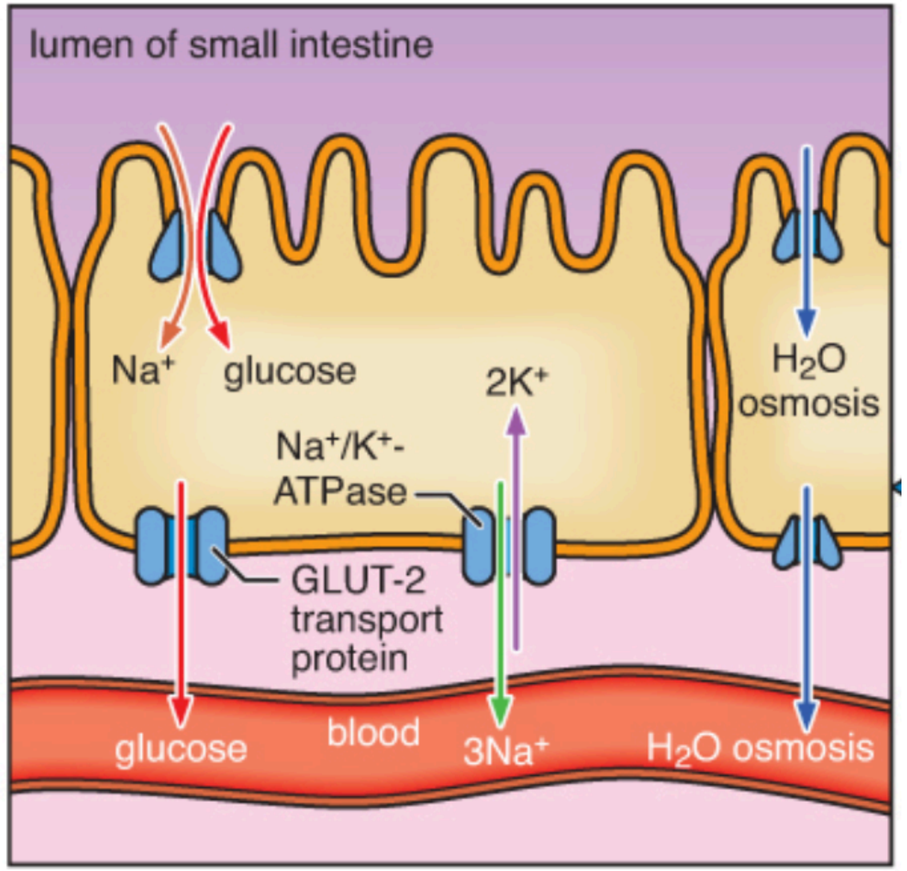
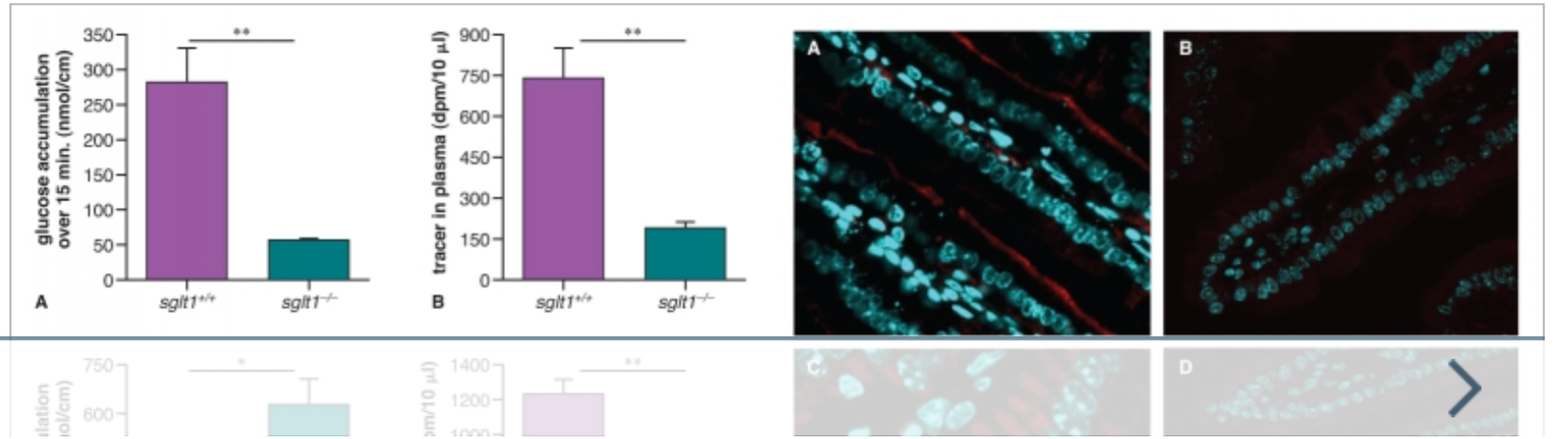




Pia Röder and her colleagues studied glucose absorption and transport in small intestine epithelial cells in mice. They took advantage of mutant strains of mice that lacked the ability to produce two transmembrane proteins known to transport glucose: the sodium-dependent glucose cotransporter (SGLT1) and glucose transporter 2 (GLUT2). {Connections: Transmembrane proteins are described in Section 7.2.} The researchers bred *sglt1* wild-type *($sglt1^{+/+}$), sglt1* mutant *($sglt1^{-/-}$), glut2* wild-type *($glut2^{+/+}$),* and *glut2* mutant *($glut2^{-/-}$)* mice.

Mice were fed a solution with radioactive ^{14}C glucose. The researchers standardized the amount given to mice based on body mass. After 15 minutes the animals were euthanized, blood was collected, and the small intestine was dissected out, everted, and washed thoroughly for analysis. Blood was centrifuged and analyzed for radioactive ^{14}C (Figure 23.7). Sections of small intestine were used to measure incorporated radioactivity, which was used to determine glucose retention (see Figure 23.7). Bio-Math Exploration 23.1 helps you understand how *p*-values were generated from the t-tests and how to interpret their significance. Sections of the epithelium of the jejunum were incubated with antibodies for SGLT1 or GLUT2 and stained for cell nuclei. This allowed the researchers to visualize localization of SGLT1 and GLUT2 along the epithelial cell membranes (Figure 23.8). In the images, you can see rows of epithelial cells that line up to form the villi of the small intestine (see also Figure 23.6). Note where SGLT1 localizes relative to the cell nuclei and how that differs from the localization of GLUT2.



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(Absorption)

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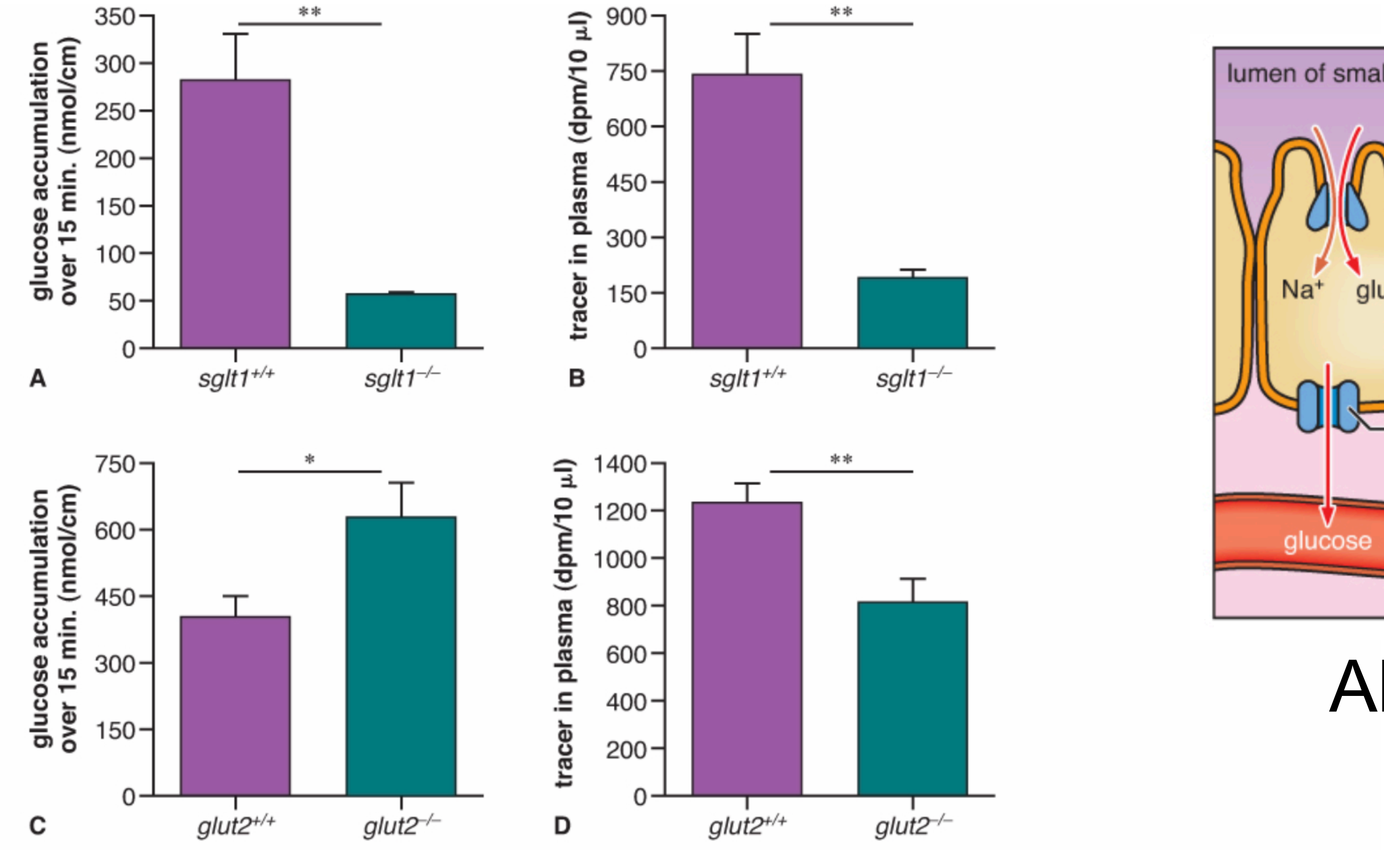
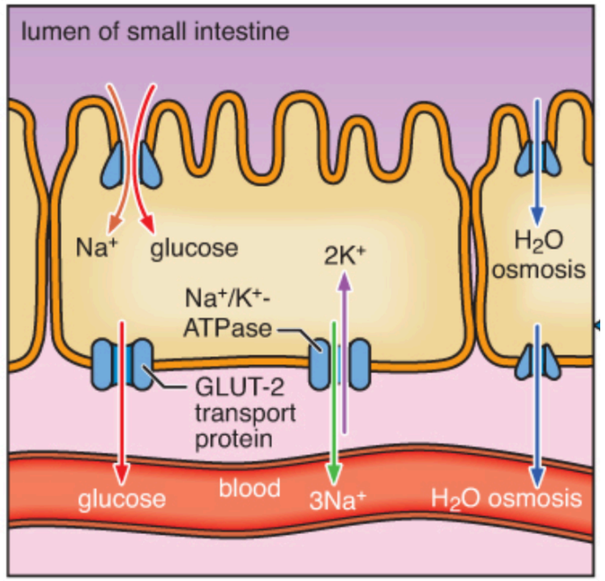




Absorption

Figure 23.7 Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose, as measured by amount of radioactive tracer. Purple bars are wild-type, and teal bars are mutant mice. **A,** Mean accumulation of glucose in intestinal tissue samples for *sglt1* wild-type and mutant mice. **B,** Mean amount of glucose in blood plasma for *sglt1* wild-type and mutant mice. **C,** Mean accumulation of glucose in intestinal tissue samples for *glut2* wild-type and mutant mice. **D,** Mean amount of glucose in blood plasma for *glut2* wild-type and mutant mice. Error bars represent ± 1 standard error (SE). Statistical analyses were performed using a t-test. *, *p*-value < 0.05; **, *p*-

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose

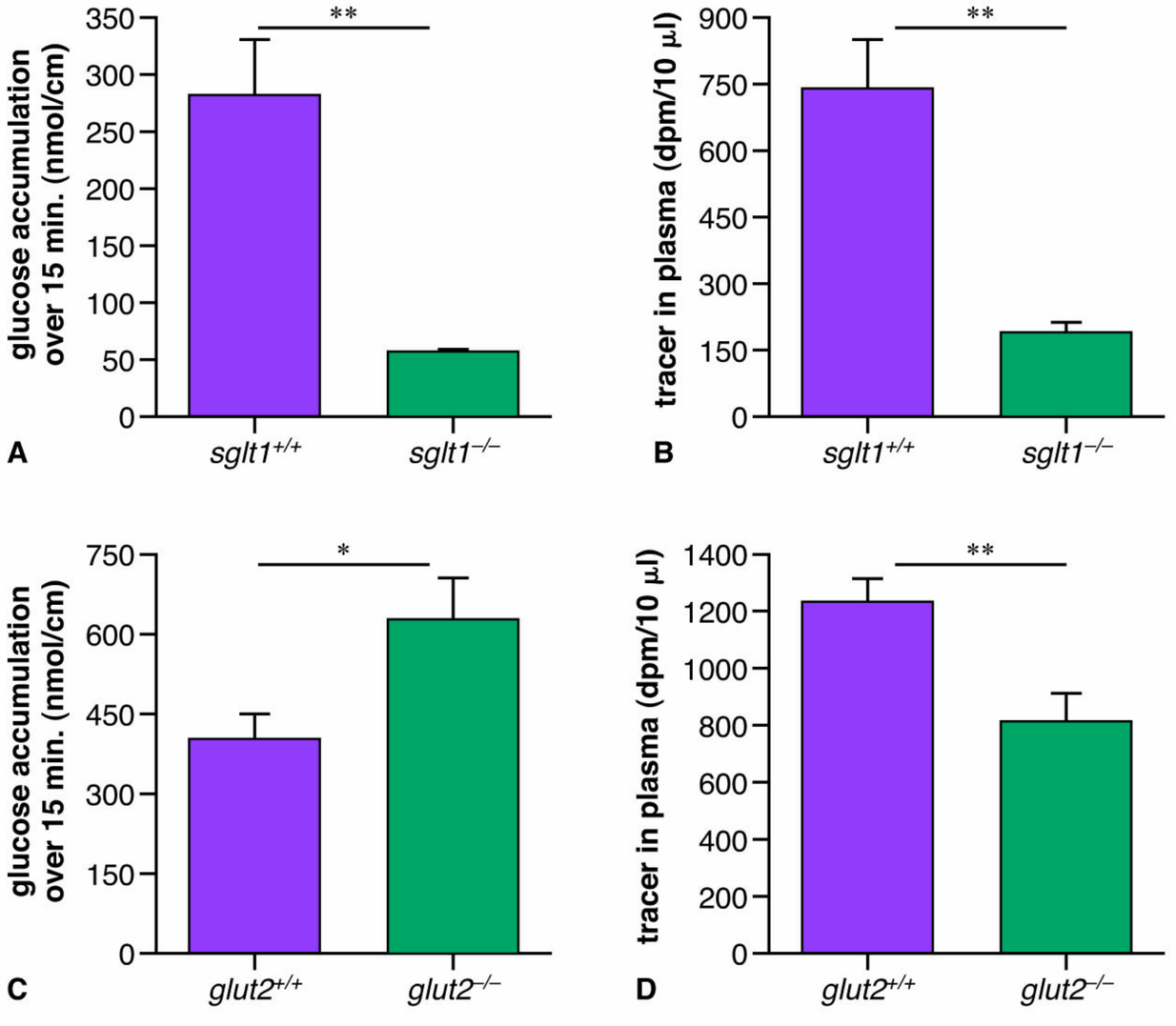


Figure 23.7

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose

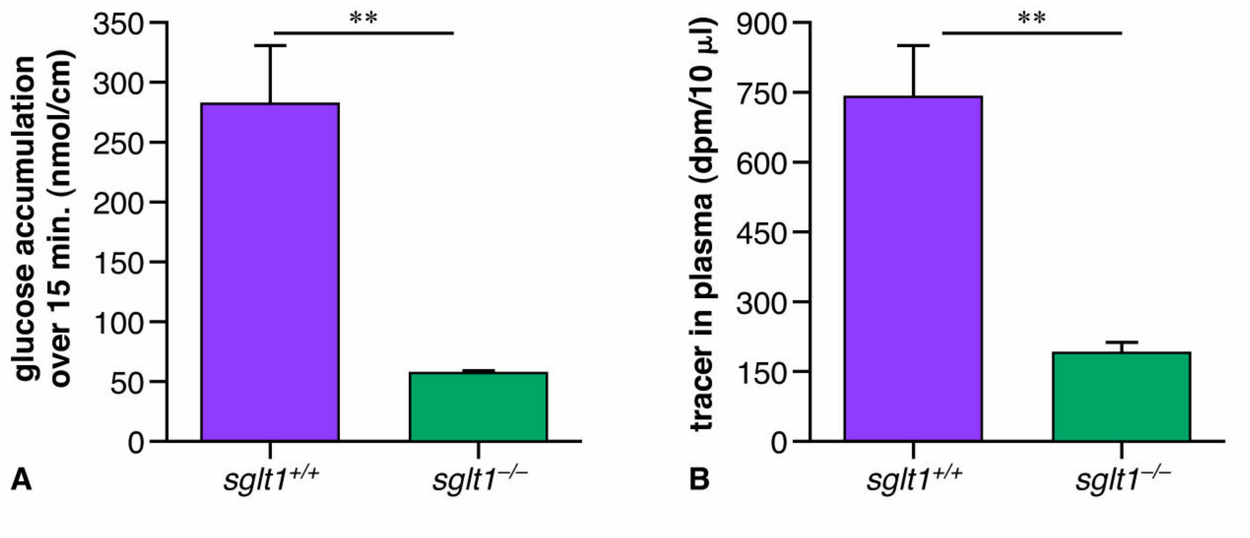
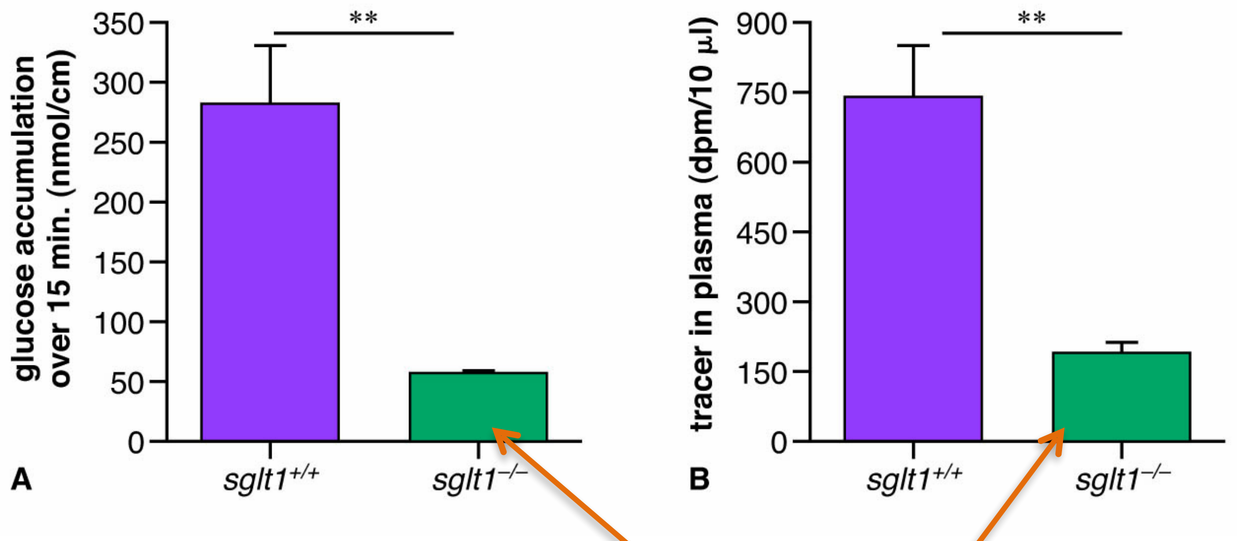


Figure 23.7

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose



Mutant *sglt1*$^{-/-}$ mice take up very little glucose into epithelial cells and show very little glucose in the blood relative to wild-type mice.

Figure 23.7

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose

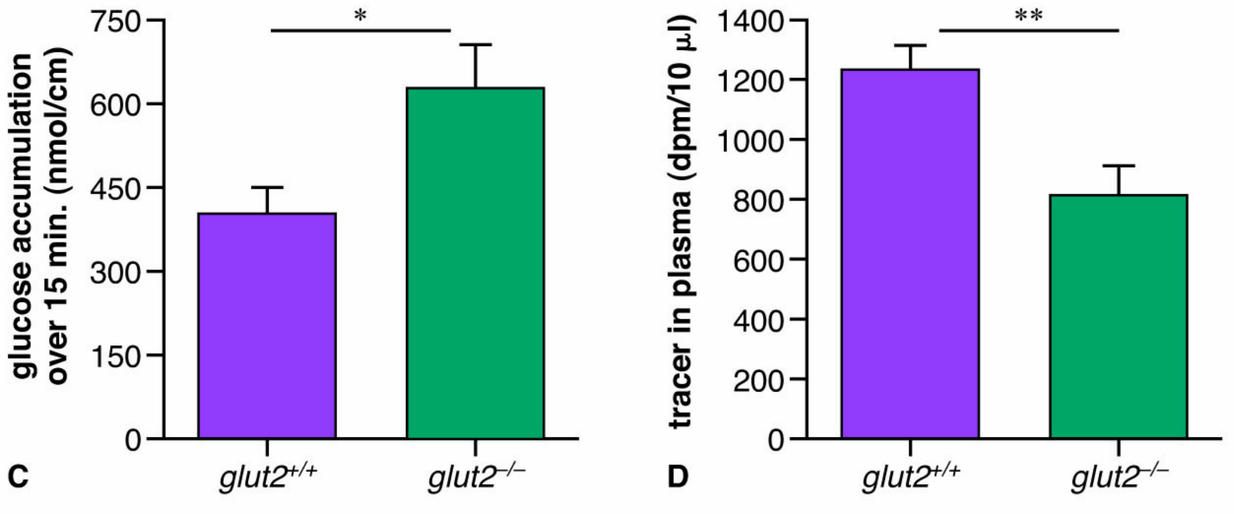


Figure 23.7

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose

Glucose accumulation is higher in mutant *glut2*$^{-/-}$ mice than wild-type mice. Glucose concentrations are lower in mutant than in wild-type mice blood.
Glucose can enter the epithelial cell but cannot get out.

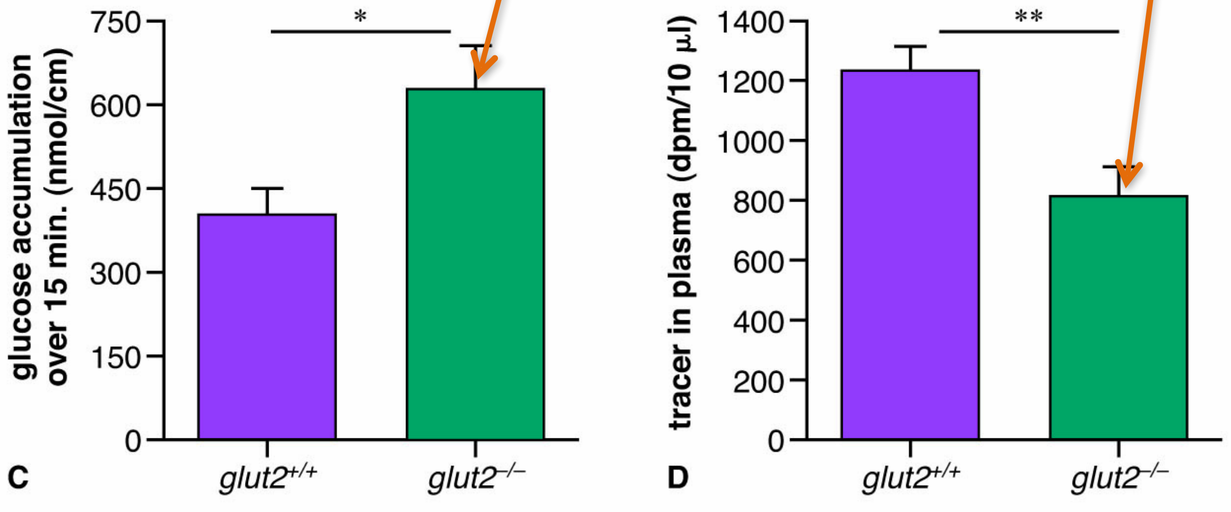


Figure 23.7

Effects of SGLT1 and GLUT2 on glucose accumulation and blood plasma glucose

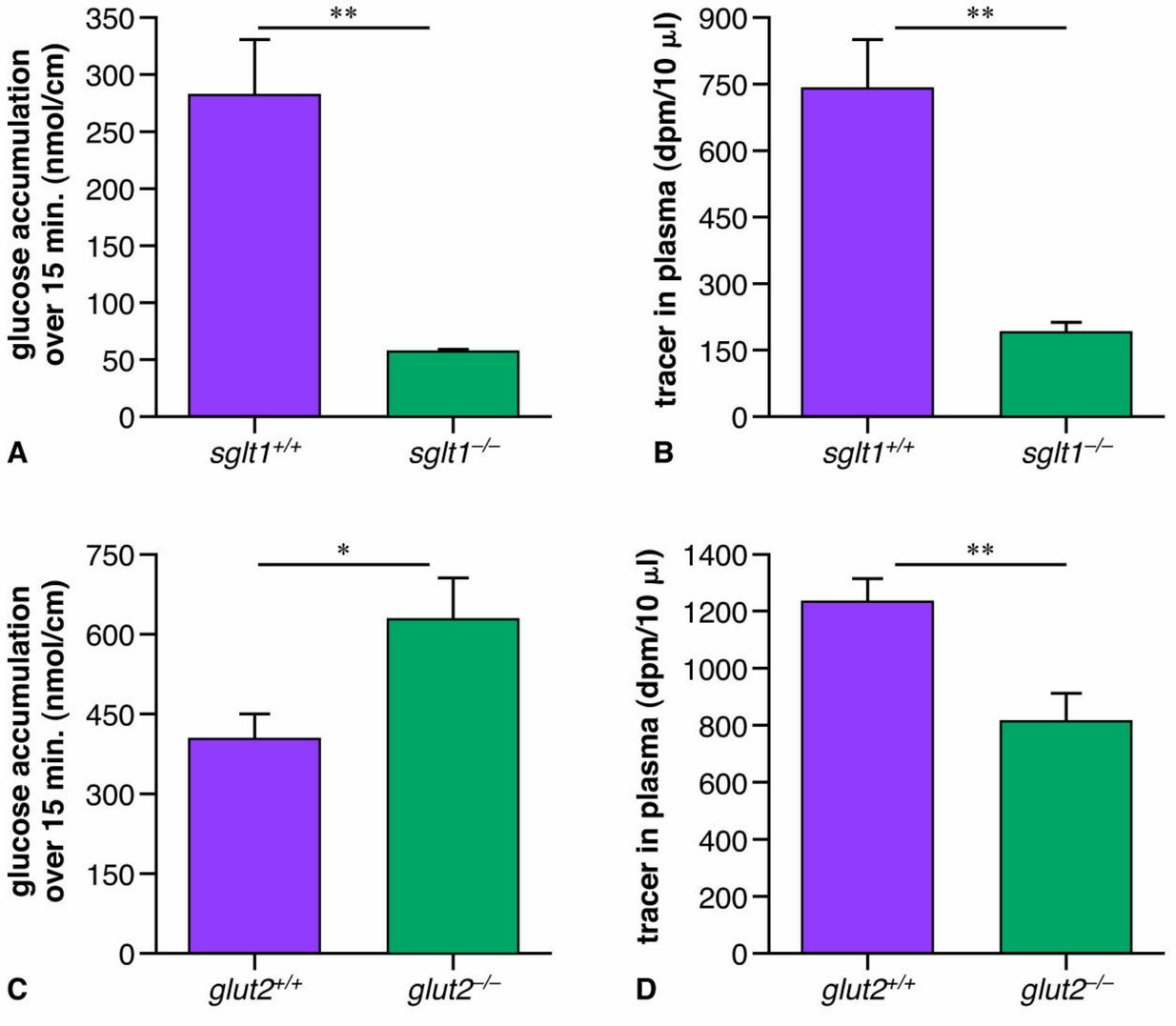


Figure 23.7

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PLOS ONE

The Role of SGLT1 and GLUT2 in Intestinal Glucose Transport and Sensing

Pia V. Röder[1], Kerstin E. Geillinger[1], Tamara S. Zietek[1], Bernard Thorens[2], Hermann Koepsell[3], Hannelore Daniel[1]*

1 ZIEL Research Center for Nutrition and Food Sciences, Biochemistry Unit, Technische Universität München, Freising, Bavaria, Germany, **2** Center for Integrative Genomics, Université de Lausanne, Lausanne, Switzerland, **3** Department of Molecular Plant Physiology and Biophysics, Julius-von-Sachs-Institute, Julius-Maximilians-Universität Würzburg, Würzburg, Bavaria, Germany

Abstract

Intestinal glucose absorption is mediated by SGLT1 whereas GLUT2 is considered to provide basolateral exit. Recently, it was proposed that GLUT2 can be recruited into the apical membrane after a high luminal glucose bolus allowing bulk absorption of glucose by facilitated diffusion. Moreover, SGLT1 and GLUT2 are suggested to play an important role in intestinal glucose sensing and incretin secretion. In mice that lack either SGLT1 or GLUT2 we re-assessed the role of these transporters in intestinal glucose uptake after radiotracer glucose gavage and performed Western blot analysis for transporter abundance in apical membrane fractions in a comparative approach. Moreover, we examined the contribution of these transporters to glucose-induced changes in plasma GIP, GLP-1 and insulin levels. In mice lacking SGLT1, tissue retention of tracer glucose was drastically reduced throughout the entire small intestine whereas GLUT2-deficient animals exhibited higher tracer contents in tissue samples than wild type animals. Deletion of SGLT1 resulted also in reduced blood glucose elevations and abolished GIP and GLP-1 secretion in response to glucose. In mice lacking GLUT2, glucose-induced insulin but not incretin secretion was impaired. Western blot analysis revealed unchanged protein levels of SGLT1 after glucose gavage. GLUT2 detected in apical membrane fractions mainly resulted from contamination with basolateral membranes but did not change in density after glucose administration. SGLT1 is unequivocally the prime intestinal glucose transporter even at high luminal glucose concentrations. Moreover, SGLT1 mediates glucose-induced incretin secretion. Our studies do not provide evidence for GLUT2 playing any role in either apical glucose influx or incretin secretion.

Citation: Röder PV, Geillinger KE, Zietek TS, Thorens B, Koepsell H, et al. (2014) The Role of SGLT1 and GLUT2 in Intestinal Glucose Transport and Sensing. PLoS ONE 9(2): e89977. doi:10.1371/journal.pone.0089977

Editor: Marià Alemany, University of Barcelona, Spain

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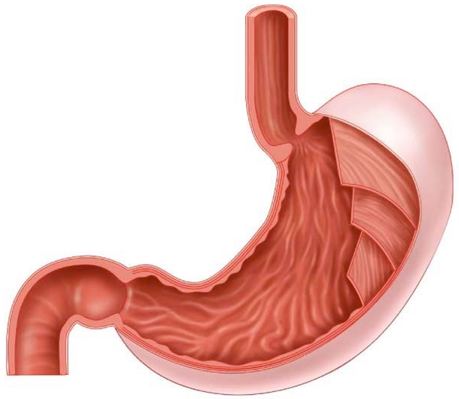
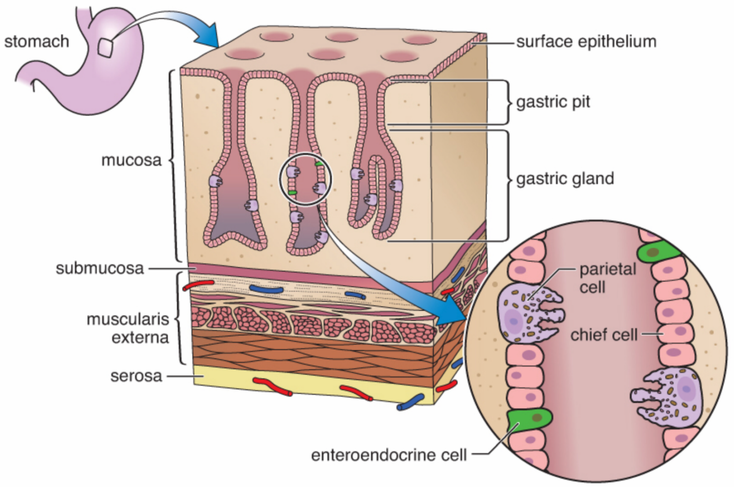
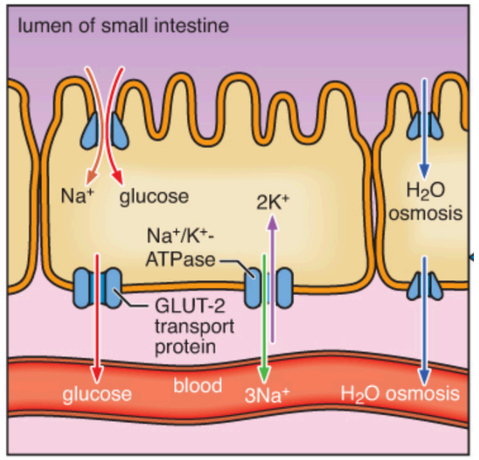
Competing Interests: The authors have declared that no competing interests exist.







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