Drug Metabolism and Disposition

META-ANALYSIS OF THE TURNOVER OF INTESTINAL EPITHELIA IN PRE-CLINICAL ANIMAL SPECIES AND HUMAN

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Supplementary data

Table 1. Enterocyte turnover in the small intestine of the rat.

Segment	Turnover (days)	SD	N	Additional information	Method	References
Stomach	2.84	0.84	6		Colchine, *in vivo*	Stevens Leblonde 1953
Proximal SI	1.24	NA	2	Postoperative controls, day 2	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal SI	1.97	NA	2	Postoperative controls, day 4	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal SI	1.71	NA	2	Postoperative controls, day 6	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal SI	2.01	NA	2	Postoperative controls, day 10	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal SI	1.86	NA	2	Postoperative controls, day 12	H-Thymidine, *in vivo*	(Menge et al., 1982)
Duodenum	1.57	NA	4		Histological study	(Leblond and Stevens, 1948)
Duodenum	1.2	0.2	4		C-glycoside, *in vivo*	(Macallan et al., 1998)
Duodenum	1.59	NA	5		BrdUrd, *in vivo*	(Qi et al., 2009)

Duodenum	1.78	NA	12	Controls	H-Thymidine, *in vivo*	(Holt et al., 1983)
Duodenum	1.98	NA	12	Rats aged 4-5 months	H-Thymidine, *in vivo*	(Holt et al., 1983)
Duodenum	2.5	NA	8		H-Thymidine, *in vivo*	(Loran and Althausen, 1960)
Duodenum	2.22	NA	6		H-Thymidine, *in vivo*	(Koldovsky et al., 1966)
Median SI	2.07	NA	2	Postoperative controls, day 2	H-Thymidine, *in vivo*	(Menge et al., 1982)
Median SI	2.3	NA	2	Postoperative controls, day 4	H-Thymidine, *in vivo*	(Menge et al., 1982)
Median SI	1.88	NA	2	Postoperative controls, day 6	H-Thymidine, *in vivo*	(Menge et al., 1982)
Median SI	1.68	NA	2	Postoperative controls, day 10	H-Thymidine, *in vivo*	(Menge et al., 1982)
Median SI	1.44	NA	2	Postoperative controls, day 12	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal jejunum	1.5	NA	5		BrdUrd, *in vivo*	(Qi et al., 2009)
Jejunum	2.29	NA	6	Non-diabetic controls	H-Thymidine, *in vivo*	(Thomson et al., 1994)
Jejunum	2.21	NA	8	Saturated fat diet	H-Thymidine, *in vivo*	(Thomson et al., 1994)
Jejunum	1.54	NA	6	Resection controls	H-Thymidine, *in vivo*	(Thomson et al., 1994)
Jejunum	2.33	NA	6	Irradiation controls	H-Thymidine, *in vivo*	(Thomson et al., 1994)
Jejunum	2.25	NA	7	20% protein	H-Thymidine, *in*	(King et al., 1983)

				diet	*vivo*	
Jejunum	2.38	NA	7	5% protein diet	H-Thymidine, *in vivo*	(King et al., 1983)
Jejunum	2.04	NA	3		H-Thymidine, *in vivo*	(Cheeseman, 1986)
Jejunum	1.3	NA	NA		NA	(Bertalanffy and Lau, 1962)
Jejunum	2.06	NA	12	Controls	H-Thymidine, *in vivo*	(Holt et al., 1983)
Jejunum	2.2	NA	12	Rats aged 4-5 months	H-Thymidine, *in vivo*	(Holt et al., 1983)
Jejunum	2.08	NA	8		H-Thymidine, *in vivo*	(Loran and Althausen, 1960)
Jejunum	2.22	NA	6		H-Thymidine, *in vivo*	(Koldovsky et al., 1966)
Jejunum	3.94	0.54	10		H-Thymidine, *in vivo*	(Shambaugh et al., 1967)
Jejunum	1.3	NaN	16		Colchine technique, *in vivo*	(Bertalanffy, 1960)
Jejunum	2.87	NA	21		H-Thymidine, *in vivo*	Uribe and Johansson 1988
Distal jejunum	1.64	NA	5		BrdUrd, *in vivo*	(Qi et al., 2009)
Distal SI	2.5	NA	2	Postoperative controls, day 2	H-Thymidine, *in vivo*	(Menge et al., 1982)
Distal SI	3.05	NA	2	Postoperative controls, day 4	H-Thymidine, *in vivo*	(Menge et al., 1982)
Distal SI	2.7	NA	2	Postoperative controls, day 6	H-Thymidine, *in vivo*	(Menge et al., 1982)

Distal SI	2.48	NA	2	Postoperative controls, day 10	H-Thymidine, *in vivo*	(Menge et al., 1982)
Distal SI	1.45	NA	2	Postoperative controls, day 12	H-Thymidine, *in vivo*	(Menge et al., 1982)
Proximal ileum	1.62	NA	5		BrdUrd, *in vivo*	(Qi et al., 2009)
Ileum	1.88	NA	6		H-Alanine and lysine uptake	(Menge et al., 1983)
Ileum	1.35	NA	4		Histological study	(Leblond and Stevens, 1948)
Ileum	1.64	NA	12	Controls	H-Thymidine, *in vivo*	(Holt et al., 1983)
Ileum	1.37	NA	12	Rats aged 4-5 months	H-Thymidine, *in vivo*	(Holt et al., 1983)
Ileum	1.6	NA	25		Vincristine, *in vivo*	(Alam et al., 1994)
Ileum	2.82	NA	8		H-Thymidine, *in vivo*	(Loran and Althausen, 1960)
Ileum	2.5	NA	6		H-Thymidine, *in vivo*	(Koldovsky et al., 1966)
Ileum	2.00	NA	NA		H-Thymidine, *in vivo*	Holle 1991
Distal ileum	1.43	NA	5		BrdUrd, *in vivo*	(Qi et al., 2009)
NA	2.1	NA	5		Colchine technique, *in vivo*	(Altmann and Enesco, 1967)
Caecum	1.04	NA	4		Vincristine, *in vivo*	Sunter 1979
Colon	3.00	NA	NA		H-Thymidine, *in*	Messier 1960

					vivo	
Colon	1.34	NA		Proximal colon, apical fold	BrdU, *in vivo*	Qi 2009
Colon	1.77	NA		Proximal colon, basal fold	BrdU, *in vivo*	Qi 2009
Colon	1.40	NA		Mid colon	BrdU, *in vivo*	Qi 2009
Colon	NA	4		Descending colon	Vincristine, *in vivo*	Sunter 1979
Colon	NA	4		Segment 2	Vincristine, *in vivo*	Sunter 1979
Colon	NA	4		Segment 3	Vincristine, *in vivo*	Sunter 1979
Colon	10.00	NA	16		Colchine, *in vivo*	Bertalanffy 1960
Colon	2.58	NA	10		H-Thymidine, *in vivo*	Finney 1989
Colon	5.42	4.20-7.50	12		H-Thymidine, *in vivo*	Sunter 1978
Colon	1.33	NA	50		Vinblastine, *in vivo*	Tutton and Barkla 1976
Rectum	6.2	NA	16		Colchine, in vivo	Bertalanffy 1960
NA=Not applicable, SI=Small intestine.						

Table 2. Enterocyte turnover in the small intestine of the mouse.

Segment	Turnover (days)	SD	N	Additional information	Method	References
Stomach	2.60	NA	NA		H-Thymidine, *in vivo*	Karam Leblond 1993
Stomach	2.98	NA	4		H-Thymidine, *in vivo*	Lee 1985
Stomach	3.11	NA	14		H-Thymidine, *in vivo*	Karam Leblond 1993b
Duodenum	2.81	0.23	16	High-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)
Duodenum	3.09	0.31	16	Low-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)
Duodenum	2.43	0.13	NA		H-Thymidine, *in vivo*	(Cheng and Bjerknes, 1982)
Duodenum	2.35	0.56	5		H-Thymidine, *in vivo*	(Merzel and Leblond, 1969)
Duodenum	3.3	NA	8		H-Thymidine, *in vivo*	(Cheng and Leblond, 1974)
Duodenum	2	NA	1		H-Thymidine, *in vivo*	(Walker and Leblond, 1958)
Duodenum	2.08	NA	6		H-Thymidine, *in vivo*	(Grey, 1968)
Duodenum	1.71	NA	20	Age: 93 days	H-Thymidine, *in vivo*	(Lesher et al., 1961)
Duodenum	2	NA	20	Age: 372 days	H-Thymidine, *in vivo*	(Lesher et al., 1961)
Duodenum	2.21	NA	20	Age: 940 days	H-Thymidine, *in vivo*	(Lesher et al., 1961)
Jejunum	3.17	0.33	16	High-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)
Jejunum	2.85	0.31	16	Low-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)

Jejunum	2.59	0.18	NA		H-Thymidine, *in vivo*	(Cheng and Bjerknes, 1982)
Jejunum	3.4	NA	8		H-Thymidine, *in vivo*	(Cheng and Leblond, 1974)
Jejunum	4	NA	20		H-Thymidine, *in vivo*	(Thompson et al., 1990)
Jejunum	1.83	NA	34	Age: 93 days	H-Thymidine, *in vivo*	(Fry et al., 1961)
Jejunum	2.17	NA	34	Age: 372 days	H-Thymidine, *in vivo*	(Fry et al., 1961)
Jejunum	2.21	NA	52	Age: 940 days	H-Thymidine, *in vivo*	(Fry et al., 1961)
Ileum	2.6	0.38	16	High-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)
Ileum	2.56	0.35	16	Low-carbohydrate diet	H-Thymidine, *in vivo*	(Ferraris et al., 1992)
Ileum	2.43	0.12	NA		H-Thymidine, *in vivo*	(Cheng and Bjerknes, 1982)
Ileum	2	NA	NA		H-Thymidine, *in vivo*	(Quastler and Sherman, 1959)
Ileum	1.29	NA	10	Age: 93 days	H-Thymidine, *in vivo*	(Fry et al., 1962)
Ileum	1.38	NA	8	Age: 372 days	H-Thymidine, *in vivo*	(Fry et al., 1962)
Ileum	1.29	NA	10	Age: 940 days	H-Thymidine, *in vivo*	(Fry et al., 1962)
Ileum	1.00	NA	23		H-Thymidine, *in vivo*	Creamer 1961
Colon	2.51	1.61	5		H-Thymidine, *in vivo*	Cheng and Bjerknes 1983
Colon	2.17	NA	5		Histological examination	Aluwihare 1971
Colon	4.85	0.94	4		H-Thymidine, *in vivo*	Tsubouchi 1981
Colon	2.42	0.11	NA		H-Thymidine, *in vivo*	Cheng and Bjerknes 1982
Colon	3.79	NA	8		H-Thymidine, *in vivo*	Chang Leblond 1971

Colon	4.96	1.24	18	Flat mucosa	Colchine, *in vivo*	Baril 1982
Colon	3.11	0.65	18	Mucosal fold tops	Colchine, *in vivo*	Baril 1982
Colon	0.67	NA	35		H-Thymidine, *in vivo*	Lipkin and Quastler 1962
Colon	0.65	NA	36		H-Thymidine, *in vivo*	De Rodriguez 1979
Colon	0.79	NA	25		H-Thymidine, *in vivo*	Thrasher 1967
Colon	1.06	NA	20		H-Thymidine, *in vivo*	Richards 1977
Colon	0.97	NA	16		H-Thymidine, *in vivo*	Chang Nadler 1975
Colon	0.97	NA	22		H-Thymidine, *in vivo*	Kovacs and Potten 1973
Colon	0.79	NA	4		H-Thymidine, *in vivo*	Potten 1974
Colon	0.67	NA	12		H-Thymidine, *in vivo*	Bottomley 1973
Colon	0.90	0.22	7		H-Thymidine, *in vivo*	Novacki 1993
Jejunum and ileum	3	NA	NA		H-Thymidine, *in vivo*	(Leblond and Messier, 1958)
Duodenum and jejunum	2-3	NA	23		H-Thymidine, *in vivo*	Creamer 1961
NA	2.67	NA	7		H-Thymidine, *in vivo*	(Smith et al., 1984)
NA=Not applicable.						

Table 3. Enterocyte turnover in the human gastrointestinal tract.

Segment	Turnover (Days)	SD	N	Additional information	Method	References
Oesophagus	6.35	2.08	1		H-Thymidine, *in vivo*	(Bell et al., 1967)
Stomach	5	1	2		H-Thymidine, *in vivo*	(Macdonald et al., 1964)
Stomach	3.5	0.5	3		H-Thymidine, *in vivo*	(Lipkin et al., 1963b)
Stomach	3.46	1.21	16	Gastric body	BrdUrd, *in vivo*	(Patel et al., 1993)
Stomach	2.58	1.17	10	Gastric antrum	BrdUrd, *in vivo*	(Patel et al., 1993)
Stomach	3.43	1.14	4		H-Thymidine, *in vivo*	(Wright et al., 1977)
Duodenum	5.42	NA	1	Individual 1	H-Thymidine, *in vivo*	(Macdonald et al., 1964)
Duodenum	5.5	0.5	1	Individual 2	H-Thymidine, *in vivo*	(Macdonald et al., 1964)
Duodenum	2	NA	56		Histological study	(Bertalanffy and Nagy, 1961)
Duodenum	1.26	0.17	2		H-Thymidine, *in vivo*	(Weinstein, 1974)
Jejunum	5	NA	3		H-Thymidine, *in vivo*	(Shorter et al., 1964)
Ileum	1.4	NA	6		Histological study	(Bullen et al., 2006)
Ileum	3	NA	3		H-Thymidine, *in vivo*	(Lipkin et al., 1963b)
Colon	1	NA	2		H-Thymidine, *in vivo*	(Lipkin et al., 1963a)
Colon	0.83	NA	3		H-Thymidine, *in vivo*	(Lipkin et al., 1963b)
Colon	3.41	NA	66		BrdUrd, *in vivo*	(Potten et al., 1992)
Colon	1.63	NA	1		H-Thymidine, *in vivo*	(Lipkin, 1969)
Colon	3.04	0.25	8		H-Thymidine, *in vitro*	(Bleiberg and Galand, 1976)
Rectum	5.5	0.5	2		H-Thymidine, *in vivo*	(Macdonald et al., 1964)
Rectum	7	1	1		H-Thymidine, *in vivo*	(Cole and Mc, 1961)

Rectum	3.66	0.42	18	Normal subjects	Histological study	(Shorter et al., 1966)
Rectum	4.73	0.59	9	Chronic ulcerative colitis in remission	Histological study	(Shorter et al., 1966)
Rectum	5.45	0.61	17	Active chronic ulcerative colitis	Histological study	(Shorter et al., 1966)
Rectum	0.83	NA	3		H-Thymidine, *in vivo*	(Lipkin et al., 1963b)
Rectum	3	NA	3		H-Thymidine, *in vivo*	(Shorter et al., 1964)
Rectum	3.5	0.5	16		H-Thymidine, *in vitro*	(Deschner et al., 1963)
Rectum	3.75	NA	8		H-Thymidine, *in vitro*	(Bleiberg et al., 1970)
NA=Not applicable						

Methods: Statistical analysis

Weighted arithmetic means (WX) were calculated utilising reported means (x_i) and sample size (n_i) of the individual studies (Equation 1). Studies reporting mean only data where n_j was not clearly stated were penalised, assuming $n_j = 1$; whereas for studies where the mean and standard deviation were reported without clearly stating n_j were assigned $n_j = 3$.

$$WX = \frac{\sum_{i=1}^{n} n_1 \cdot X_i}{\sum_{i=1}^{n} n_i}$$

Equation 1

The combined standard deviation (overall SD) was obtained through the calculating the total sum of squares (overall SS) (Equation 2 and Equation 3).

$$Overall\ SS = \sum_{i=1}^{n} [(SD_i^2 + X_i^2) + n_i] - N \cdot WX^2$$

Equation 2

$$Overall\ SD = \sqrt{\frac{Overall\ SS}{N}}$$

Equation 3

The geometric mean (GM) and standard deviation (GSD) of the enterocyte turnover was calculated by calculating σ (lnSD; Equation 4 and Equation 5) and using the reported mean and variance and μ (lnGM; Equation 6 and Equation 7).

$$\sigma = \sqrt{\ln\left(\frac{variance}{X^2} + 1\right)}$$

Equation 4

$$GSD = e^{\sigma}$$

Equation 5

$$\mu = lnX - \frac{1}{2} \cdot ln\left(\frac{1}{2} \cdot \sigma^2\right)$$

Equation 6

$$GM = e^{\mu}$$

Equation 7

Statistical analysis was carried out using Welch's t test (P<0.05) with post-hoc Dunn-Šidák correction in Matlab® R2010a (Mathworks, Natick, USA), using the sample means (X), size (n) and standard deviations (s^2), where data allowed (Equation 8).

$$t = \frac{X_1 - X_2}{\sqrt{\frac{s_1^2}{N_1} - \frac{s_2^2}{N_2}}}$$

Equation 8

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