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Potentiation of serotonin signaling leads to increased carbohydrate and lipid absorption in the murine small intestine

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ABSTRACT

Background: Enteric serotonin influences intestinal homeostasis and functions as a mucosal growth factor. Previously, we demonstrated increased mucosal surface area and enhanced crypt cell proliferation in serotonin reuptake transporter (SERT)-deficient mice. Therefore, we hypothesized that serotonin-mediated mucosal growth would also result in enhanced carbohydrate and lipid absorption.

Material and methods: Wild-type C57Bl/6 (WT) and SERT-knockout (SERTKO) mice were fasted then gavaged with D-xylose or boron-dipyrromethene (BODIPY) FL-C12 medium-chain fatty acid analog. Serum D-xylose and BODIPY concentrations were serially measured from blood drawn at 30 to 360 min post-gavage. Small intestine was harvested from both groups for comparison of morphometric parameters. Area under the curve of plotted graphs was calculated, and means were compared with Student's *t*-test to a significance of $p < 0.05$.

Results: Villus height and crypt depth were significantly greater in the middle and distal small intestine of SERTKO animals compared to WT. Overall absorption of D-xylose and BODIPY was greater in SERTKO animals compared to WT animals. Absorption of D-xylose was persistently elevated in SERTKO animals, while there was an initial delay in BODIPY absorption followed by a sustained and significantly greater absorption in SERTKO animals at 60–360 min after gavage.

Conclusion: Potentiation of serotonin signaling in SERTKO mice results in small intestinal mucosal growth and enhanced carbohydrate and fat absorption in vivo. These functional increases support the concept of targeting the serotonin signaling system to augment intestinal adaptation in the setting of intestinal failure.

Serotonin (5-HT) is a monoamine that functions as a paracrine messenger, endocrine hormone and neurotransmitter on a wide range of target organs [1]. While best known for its actions in the central nervous system (CNS), approximately 95% of the body's 5-HT is produced and retained in the gastrointestinal (GI) tract [1,2]. Biosynthesis of 5-HT primarily occurs in enterochromaffin (EC) cells of the intestinal mucosa and depends on the rate limiting enzyme tryptophan hydroxylase 1 (TPH1) [2,3]. A separate gene product, tryptophan hydroxylase 2 (TPH2), mediates the less abounding biosynthesis of 5-HT in neurons of the CNS and enteric nervous system (ENS) [2,3].

While serotonin participates in reflex activity in the GI tract [4,5], free 5-HT in large quantities is toxic and may mediate anaphylactic shock [6]; therefore, local inactivation of 5-HT is paramount and primarily accomplished through transmembrane transport by the high-affinity serotonin reuptake transporter (SERT; 5-HTT) [7]. SERT is expressed by intestinal epithelial cells, 5-HT-producing neurons and circulating platelets and is inhibited by selective serotonin reuptake inhibitors (SSRIs) [1,2].

A mouse model with a targeted deletion of SERT (SERT knock-out; SERTKO) has been an invaluable tool to study the effects of diminished 5-HT inactivation and potentiated 5-HT signaling in the laboratory setting. Homozygous SERTKO mice are viable and exhibit normal development and weight gain [8,9]. Although prior studies of SERTKO mice have shown some phenotypic changes including increased anxiety and decreased aggression [10], the effects on gut function are relatively minor and are limited to increased stool water content and alternating rapid and slow transit [11].

In concordance with the idea that serotonin can act as a growth factor [12–16], mucosal architecture of SERTKO mice is altered and exhibits taller villi, deeper crypts and increase in crypt cell proliferation leading to increase in mucosal surface area (MSA) [17–19]. Further, the normal cellular composition of intestinal villi is preserved in SERTKO mice, indicating that the mucosa resulting from enhanced 5-HT signaling should retain its original absorptive function [19]. However, the

Abbreviations: 5-HT, serotonin; CNS, central nervous system; GI, gastrointestinal; EC, enterochromaffin; TPH1, tryptophan hydroxylase1; TPH2, tryptophan hydroxylase 2; ENS, enteric nervous system; SERT, serotonin reuptake transporter; SSRI, selective serotonin reuptake inhibitor; KO, knock-out; MSA, mucosal surface area; WT, wild-type; BODIPY, boron-dipyrromethene; MCFA, medium chain fatty acid; SCFA, short chain fatty acid; LCFA, long chain fatty acid; AUC, area under the curve; RFU, relative fluorescence units; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; FATP, fatty acid transport protein.

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absorptive capacity of the intestinal mucosa in SERTKO mice has not yet been examined. Based on previous findings of increased intestinal mucosal surface area and preserved cellular composition of villi, we hypothesized that SERTKO mice have enhanced in vivo absorption of macromolecules such as carbohydrates and lipids.

1. Material and methods

1.1. Animals

Wild-type (WT) and SERTKO mice were bred on C57Bl/6 background at The Jackson Laboratory (Farmington, CT) and transferred to Yale University. Mice were housed under pathogen-free conditions on a 12-h dark/light cycle with food and water ad libitum. Lineage of SERTKO mice was produced first by breeding WT and SERT −/− mice to produce heterozygous SERT +/−. SERT −/− females have been observed to neglect their pups, therefore SERT −/− males and heterozygous SERT +/− females were bred for the production of SERT −/− offspring. Genotype was determined by KAPA HotStart Mouse Genotyping kit (Kapa Biosystems, Wilmington, MA) per manufacturer instructions. Primers [20] were acquired from the Yale University School of Medicine W.M. Keck Oligonucleotide Synthesis Facility (Table 1). 8–18 week-old mice of both genders were used for experiments. At the end of the treatment period, mice were euthanized by CO2 asphyxiation and subsequent cervical dislocation. Animal protocols were approved by Yale University's Institutional Animal Care and Use Committee (IACUC #: 2016–11,567).

1.2. Carbohydrate absorption

WT (n = 7) and SERTKO (n = 7) mice were fasted for 4 h then gavaged with 100 μl of 2 g/kg body weight D-xylose (Sigma-Aldrich, St. Louis, MO; dissolved in deionized water). D-xylose, a five-carbon monosaccharide, is absorbed by enterocytes independently of digestive enzymes and rely only on intact small intestinal mucosa [21]. It is commonly used in the clinical setting to assess mucosal integrity in order to elucidate the cause for malabsorption. Blood was collected at 30, 60, 120, 240 and 360 min after gavage and serum D-xylose levels were quantified spectrophotometrically utilizing a D-xylose assay kit (Chondrex, Redmond, WA).

1.3. Lipid absorption

WT (n = 5) and SERTKO (n = 5) mice were fasted for 4 h then received 100 μl of 1.5 mg/kg body weight boron-dipyrromethene (BODIPY) FL-C12 medium-chain fatty acid analog (Life Technologies Corporation, Carlsbad, CA; resuspended in DMSO) by oral gavage. For this study, a 12-carbon medium-chain fatty acid (MCFA) analog was chosen based upon how different length fatty acid chains are absorbed. Short-chain fatty acids (SCFA), which have a chain length of one to six carbons, are partially metabolized in the GI wall and thus, a part of the absorbed SCFA never reaches the plasma [22]. Long-chain fatty acids (LCFA), comprised of more than 14 carbons, are predominantly incorporated into chylomicrons and transported through the lymphatic system [23,24]. In contrast, MCFA consisting of 6 to 12 carbons primarily enter the portal circulation bound to albumin and up to 70% of fatty acids with 12 carbons can be recovered in the plasma [25]. Thus, these MCFA are the optimal lipid to use when studying mucosal absorption. Additionally, the BODIPY fluorophore itself is intrinsically lipophilic and probes incorporating this fluorophore undergo native-like transport and metabolism in cells [26]. Serum BODIPY FL-C12 concentrations were serially measured from blood drawn at 30, 60, 120, 240 and 360 min after gavage and quantified by measuring fluorescence at excitation 488 nm and emission 515 nm.

Table 1
Primers used for genotyping SERTKO mice [20].

Primer type	Sequence 5′➔3′
Mutant reverse	GCC AGA GGC CAC TTG TGT AG
Common	AAT GGT GAG GAG TGG TGG AG
Wild type reverse	CCT AGA TAC CAG GCC CAC AA

1.4. Bowel harvest

To compare small intestine morphometric parameters, WT (n = 3) and SERTKO (n = 3) mice were euthanized by CO2 asphyxiation and cervical dislocation. The small intestine was identified from the ligament of Treitz to ileocecal valve and harvested by sharp dissection. The bowel was flushed with 10% neutral buffered formalin (NBF) and 2 cm segments of proximal, middle and distal small bowel were isolated and fixed in 10% NBF for at least 12 h before paraffin embedding and mounting on slides.

1.5. Anatomical measurement of mucosal parameters

Paraffin sections underwent standard hematoxylin & eosin staining. The slides were examined at 200–400× using standard brightfield microscopy (Axio Imager M1, Zeiss, OberKochen, Germany) and analyzed using ImageJ software (NIH, Bethesda, MD). Villi were measured only when intact from crypt-villus junction to crypt-villus junction with a visible central lacteal. Crypts were measured when intact from crypt-villus junction to crypt-villus junction and with at least partial visualization of adjacent villi. At least thirty villi and fifteen crypts were measured per animal.

1.6. Statistical analysis

Total area under the curve (AUC) of plotted graphs was calculated using GraphPad Prism version 7.0a for MAC OS X (Graphpad Software, La Jolla, CA). Means were compared with Student's *t*-test to a significance of $p < 0.05$.

2. Results

2.1. Small intestine mucosal parameters of SERTKO vs WT

In the middle and distal small intestine, villus height (VH) and crypt depth (CD) were significantly greater in SERTKO animals compared to WT littermates ($p < 0.01$ for all comparisons; Table 2 & Fig. 1A-D). In the proximal small bowel, there was no difference in VH but CD was significantly greater in SERTKO mice compared to WT ($p = 0.03$).

2.2. D-xylose absorption

At every time point measured, mean serum D-xylose levels were higher in SERTKO mice compared to WT littermates (Fig. 2A). Mean ± SEM serum D-xylose levels in SERTKO mice were 3.5 ± 0.5 μM, 2.9 ± 0.4 μM, 2.1 ± 0.3 μM, 1.7 ± 0.4 μM, 1.1 ± 0.02 μM at 30, 60, 120, 240 and 360 min after gavage respectively. Mean ± SEM serum D-xylose levels in WT mice were 3.2 ± 0.2 μM, 2.6 ± 0.2 μM, 1.7 ± 0.1 μM, 1.1 ± 0.1 μM, 1.0 ± 0.1 μM at 30, 60, 120, 240 and 360 min after gavage respectively. AUC of the plotted graph was significantly greater for

Table 2
Comparison of mean ± SEM values of VH and CD between WT and SERTKO mice.

		WT	SERTKO	p-Value
VH	Proximal (μm)	410.3 ± 6.9	419.2 ± 6.8	0.36
	Middle (μm)	212.4 ± 4.8	240.7 ± 5.2	**0.0002**
	Distal (μm)	182.8 ± 4.3	201.2 ± 3.3	**0.005**
CD	Proximal (μm)	78.8 ± 1.5	89.6 ± 4.9	**0.03**
	Middle (μm)	72.2 ± 1.6	101 ± 10.3	**0.01**
	Distal (μm)	77.4 ± 2.0	96.3 ± 3.0	<**0.0001**

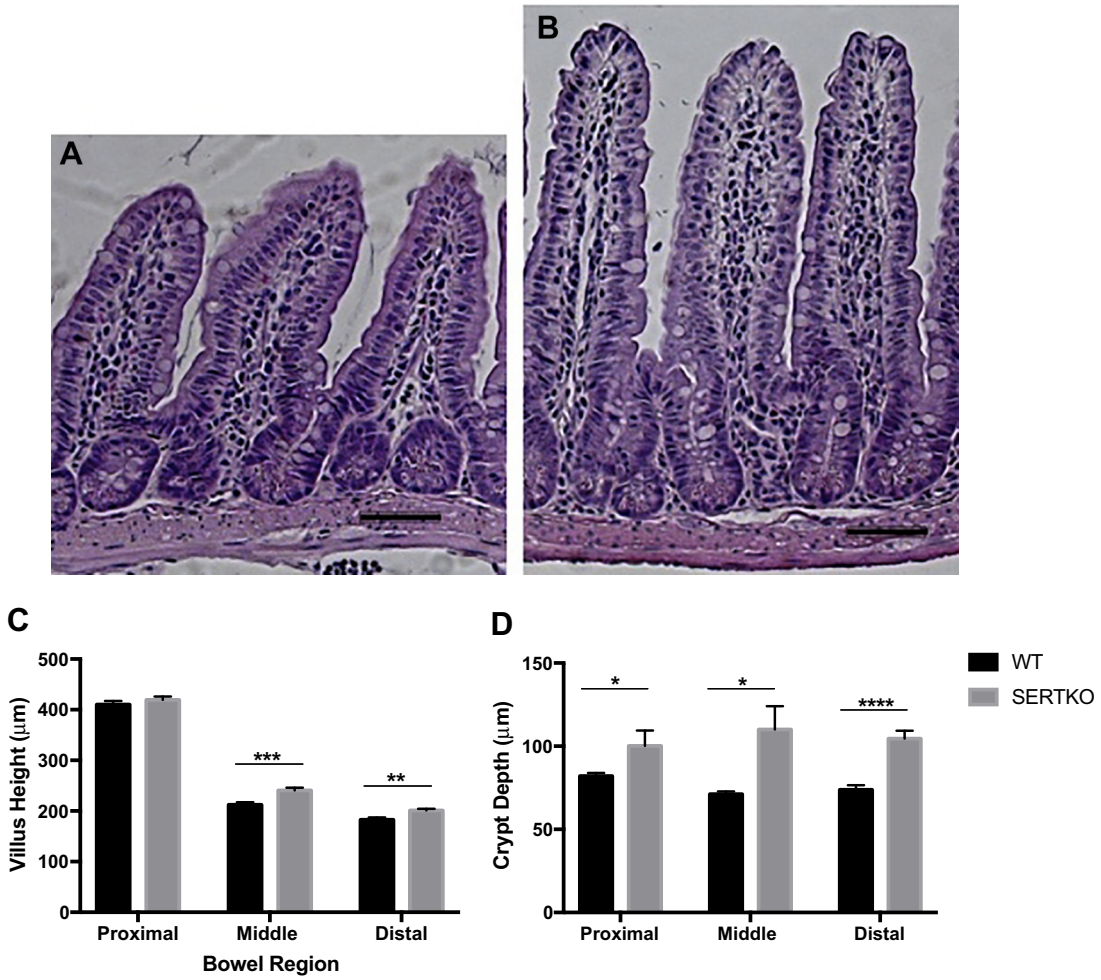

Fig. 1. SERTKO mice have increase in small intestine mucosal parameters. *(A)* Mucosal architecture in a section of WT mice ileum stained with H&E. *(B)* Mucosal architecture in a section of SERTKO mice ileum stained with H&E. *(C)* VH of proximal, middle and distal small intestine comparing WT vs. SERTKO mice. *(D)* CD of proximal, middle and distal small intestine comparing WT vs. SERTKO mice. *A-B scale bars:* 50 μm.

SERTKO mice compared to WT littermates (516.3 ± 41.1 vs. 418.7 ± 14.5; p = 0.045, Fig. 2B).

2.3. BODIPY FL-C12 absorption

Mean serum BODIPY FL-C12 level was significantly greater in WT littermates compared to SERTKO animals at 30 min after gavage (WT 32877 ± 3390, SERTKO 17531 ± 2330; p = 0.006). At every subsequent time point measured, mean serum BODIPY FL-C12 levels were higher in SERTKO mice compared to WT littermates (Fig. 3A). Mean ± SEM BODIPY FL-C12 relative fluorescence units (RFU) in SERTKO mice were 26,851 ± 5686, 16,614 ± 2923, 15,328 ± 3139, 22,265 ± 6531 at 60, 120, 240 and 360 min after gavage respectively. Mean ± SEM BODIPY FL-C12 RFU in WT mice were 19,257 ± 4887, 10,427 ± 2060, 11,104 ± 3207, 12,668 ± 4073 at 60, 120, 240 and 360 min after gavage respectively. AUC of the plotted graphs was greater for SERTKO compared to WT but did not reach statistical significance ($5.3 \times 10^6 \pm 1.0 \times 10^6$ vs. $4.0 \times 10^6 \pm 5.6 \times 10^5$; p = 0.28, Fig. 3B). Similarly, there was greater total BODIPY absorption in SERTKO mice compared to WT but did not reach statistical significance (19,496 ± 1897 vs. 17,666 ± 2360; p = 0.55). However, when comparing late (60–360 min after gavage) absorption, SERTKO mice had significantly greater serum BODIPY FL-C12 compared to WT mice (20,042 ± 2348 vs. 13,441 ± 1906; p = 0.04, Fig. 3C).

3. Discussion

Here, we present a functional adjunct to previously reported small intestinal morphologic changes seen in SERTKO mice, a model of potentiated 5-HT signaling. We confirm these morphometric changes and further demonstrate enhanced in vivo absorption of simple carbohydrates and MCFA in SERTKO mice compared to WT littermates. While there was a steady drop in serum D-xylose levels over the time period for both study groups, serum levels were consistently higher in SERTKO mice compared to WT from 30 min to 360 min post-gavage. In contrast, when gavaged with MCFA, SERTKO mice displayed an initial delay followed by a prolonged enhancement in absorption compared to WT littermates. Serum BODIPY levels in SERTKO mice also displayed a nadir at 120–240 min post-gavage with an uptrend at 360 min. While there was no significant difference in total BODIPY absorption during the 6-h experiment, it is possible that BODIPY levels in SERTKO animals may remain elevated for a prolonged period of time and may be delineated by future experiments with longer duration. Overall, these findings provide important data to support the functional enhancements that can parallel mucosal growth seen in SERTKO mice.

The kinetics of carbohydrate and lipid absorption differed in this study. The different patterns of serum D-xylose and BODIPY FL-C12 absorption in SERTKO mice seen in this study may be partially explained by the respective macronutrient's effect on gastric emptying. The absorption of D-xylose was a linear curve while absorption of BODIPY

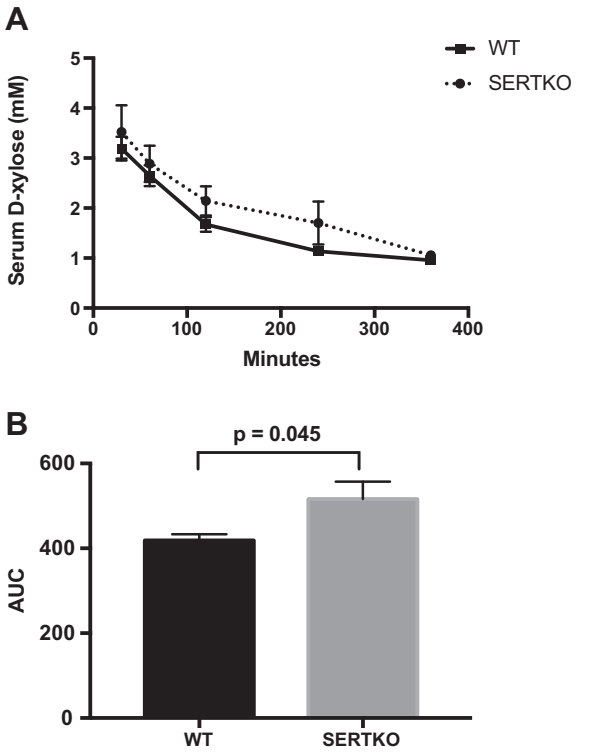

Fig. 2. SERTKO mice have enhanced in vivo D-xylose absorption. *(A)* Plotted graph of mean ± SEM serum D-xylose levels measured at 30, 60, 120, 240 and 360 min after gavage. *(B)* AUC of graph 'A' showing significantly greater D-xylose absorption by SERTKO compared to WT mice.

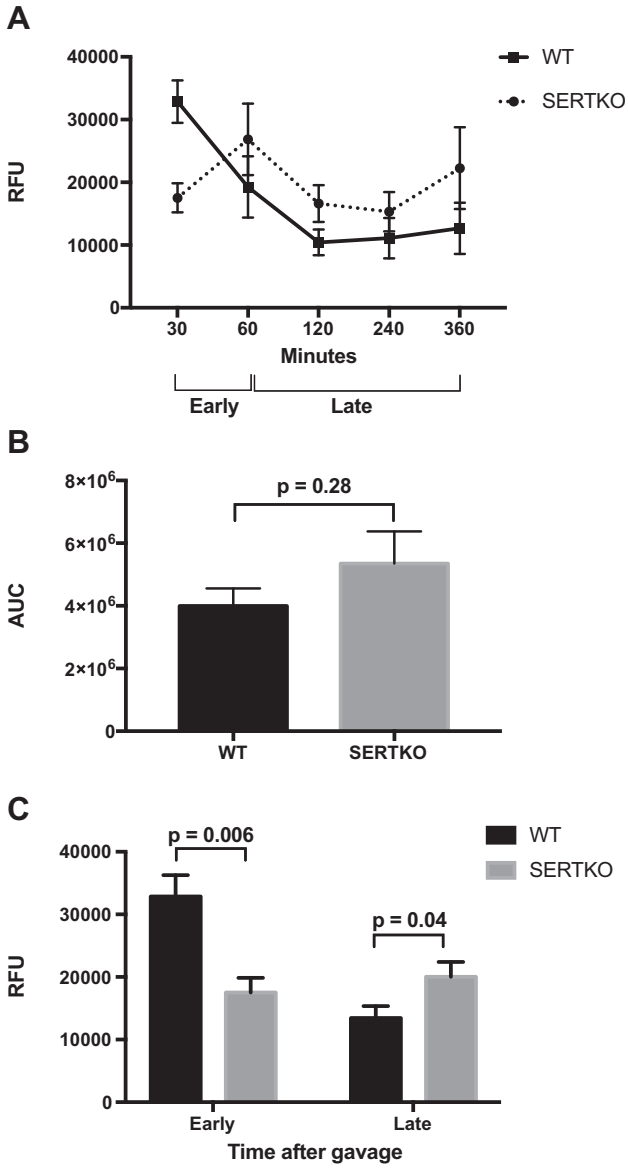

Fig. 3. SERTKO mice have an initial delay followed by a prolonged enhancement in in vivo BODIPY FL-C12 absorption. *(A)* Plotted graph of mean ± SEM BODIPY FL-C12 RFU measured at 30, 60, 120, 240 and 360 min after gavage. *(B)* AUC of graph 'A' showing no difference in total absorption between WT and SERTKO mice. *(C)* Early (30 min post-gavage) vs. late (60–360 min post-gavage) absorption of BODIPY FL-C12.

FL-C12 showed a sinusoidal pattern in the SERTKO mouse. In studies whereby different macronutrients are infused into the stomach or small intestine, gastric emptying is delayed in response to the release of postprandial gastrointestinal hormones such as glucagon-like peptide-1 (GLP-1) and cholecystokinin (CCK), with fat having the most substantial effect [27,28]. In particular, CCK, which is an important inhibitory regulator of gastric motility, is postulated to be stimulated by the formation of chylomicrons and its effects are mediated by fatty acids of 12 carbons or more [29,30]. In a study examining the absorption of different length chain fatty acids in rats, 72% of lauric (12:0) acid bypassed the lymphatic pathway [25]. Therefore, while the majority of the BODIPY FL-C12 likely entered the portal circulation, it is reasonable to speculate that at least a portion was taken up by chylomicrons, stimulating the release of CCK.

Moreover, there is evidence that gastric emptying may be fundamentally delayed in the setting of potentiated 5-HT signaling. Li et al. demonstrated significantly faster gastric emptying in mice lacking TPH2, the rate limiting enzyme for biosynthesis of neuronal 5-HT [31]. While TPH1KO mice did not show significant difference in gastric emptying compared WT animals, TPH1/2 double knock-out mice exhibited similar patterns of rapid gastric emptying as TPH2KO mice. With regards to 5-HT signaling, SERTKO and TPH1/2KO animals lie on opposing sides of the spectrum; therefore, it is possible that gastric emptying in SERTKO mice is delayed. The combination of the slowing of gastric emptying by ingestion of lipids with the intrinsically delayed gastric emptying in SERTKO may result in the pattern of lipid absorption we see in our present study.

Additionally, whereas transport across the mucosal border is completely diffusional for D-xylose [32], uptake of fatty acids is much more complex and dependent on the formation of micelles, bile acids and fatty acid transport proteins (FATP) [33]. Such transport proteins in SERTKO mice have not yet been characterized and may affect the pace of fatty acid uptake. Further, based on recent evidence suggesting that SERTKO mice exhibit impaired regulation of insulin signaling and are more susceptible to liver steatosis [34], it is also plausible that SERTKO mice may have alterations in their biliary physiology.

Other factors to consider are the effects of potentiated serotonin signaling in the gut microbiota. Accumulating evidence suggests a role for the gut microbiome in the regulation of intestinal metabolism, including host production of signaling molecules such as serotonin [35]. The microbiota of the small intestine is also known to modulate host intestinal adaptation by microbial-derived metabolites [36]. At the present, the microbiota composition of SERTKO mice is unknown, as are the effects of such changes in the intestinal flora on mucosal proliferation and absorptive function.

Finally, the effects mediated by changes to mucosal barrier function in the setting of potentiated serotonin signaling cannot be ignored. Serotonin has been shown to raise cyclic adenosine monophosphate (cAMP) levels in isolated goldfish intestinal mucosa, thereby increasing bidirectional Cl^- fluxes [37]. Additionally, healthy individuals ingesting oral 5-HT demonstrated biochemical evidence for reinforcement of

intestinal barrier function, while this reinforcement appeared to be impaired in patients with irritable bowel syndrome (IBS) [38]. The implications of these findings are unclear, but nonetheless, highlight the complexity of the serotonergic system in the GI tract.

Despite these uncertainties, the findings of our study indicate that an increase in absorptive capacity accompanies the known morphological changes observed in SERTKO mice. Such changes, particularly taller villi, deeper crypts and increase in crypt cell proliferation, are hallmark features of intestinal adaptation following bowel resection in both humans and animal models [39]. Further, pharmacological blockade of SERT with SSRIs or treatment of WT mice with 5-HT agonists produce similar anatomical changes [17,40]. Clinical implications of these findings are important for patients who would benefit from enhanced intestinal adaptation, such as those who are dependent on parenteral nutrition due to inadequate bowel length. A short bowel animal model would serve as the next step to investigate the role of potentiated serotonin signaling in augmenting the native intestinal adaptation process.

4. Conclusions

SERTKO mice have enhanced in vivo absorptive capacity of simple carbohydrates and MCFA during a controlled six-hour experiment. This is a finding that parallels the morphologic changes seen in SERT-deficient mice, such as increase in mucosal proliferation and larger mucosal surface area. While further studies elucidating the exact absorptive mechanisms are warranted, potentiation of serotonin appears to stimulate growth of functional small intestinal mucosa and may be an attractive target of therapy for gastrointestinal malabsorptive disorders such as intestinal failure.

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