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Soluble epoxide hydrolase as a therapeutic target for obesity-induced disorders: roles of gut barrier function involved

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Abstract

Emerging research supports that soluble epoxide hydrolase (sEH), an enzyme involved in eicosanoid metabolism, could be a promising target for obesity-associated disorders. The sEH enzyme is overexpressed in many tissues of obese animals. Genetic ablation or pharmacological inhibition of sEH attenuates the development of a wide range of obesity-induced disorders, including endoplasmic reticulum stress, metabolic syndrome, kidney diseases, insulin resistance, fatty liver, hepatic steatosis, inflammation, and endothelial dysfunction. Furthermore, our recent research showed that genetic ablation or inhibition of sEH attenuated obesity-induced intestinal barrier dysfunction and its resulted bacterial translocation, which is widely regarded to be a central mechanism for the pathogenesis of various obesity-induced disorders. Together, these results support that targeting sEH could be a promising strategy to reduce risks of obesity-induced disorders, at least in part through blocking obesity-induced leaky gut syndrome.

Keywords

Soluble epoxide hydrolase; obesity; gut microbiota; intestinal barrier function

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Introduction

Obesity, which is defined by body mass index (BMI) over 30, is a serious health problem in Western countries [1, 2]. It was estimated that >35% adults and >17% children in the United States are obese [1, 2]. Obese individuals have increased risks of developing many chronic diseases, including metabolic diseases, diabetes, cardiovascular diseases, and several types of cancers [3]. For example, colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death in the United States [4], and previous studies have shown that obese individuals have 30-60% greater risk of developing CRC [5, 6]. It is of critical importance to identify novel therapeutic targets for obesity-induced disorders, in order to develop novel strategies for prevention and/or treatment.

Recent research supports that soluble epoxide hydrolase (sEH), an enzyme involved in eicosanoid metabolism, could be a promising therapeutic target for obesity-associated disorders. The expression and activity of sEH, as well as the concentrations of sEH-produced lipid metabolites, have been shown to be increased in tissues of obese animals [7-10]. Genetic ablation or pharmacological inhibition of sEH attenuates the development of various obesity-induced disorders, including endoplasmic reticulum (ER) stress, metabolic syndrome, insulin resistance, fatty liver, hepatic steatosis, inflammation, and endothelial dysfunction [11-19]. More importantly, our recent research showed that genetic ablation or inhibition of sEH abolished obesity-induced intestinal barrier dysfunction and bacterial translocation [20], which is widely regarded as a central mechanism for the pathogenesis of various obesity-induced disorders [21-23]. Together, these results suggest a novel theme that targeting sEH could attenuate risks of various obesity-induced disorders, at least in part through blocking obesity-induced leaky gut syndrome. Therefore, sEH could be an important therapeutic target for preventing and/or treating a wide range of obesity-induced chronic diseases. This is clinically important because pharmacological inhibitors of sEH have been evaluated in multiple human clinical trials targeting other disorders [24, 25], and could be explored to target obesity-induced disorders.

In this review, we will discuss the biochemistry of sEH-mediated eicosanoid metabolism and the functional roles of sEH in regulating obesity-induced disorders. Moreover, we will discuss our recent finding which suggests that targeting sEH could attenuate various obesity-induced disorders through blocking obesity-caused intestinal barrier dysfunction.

1. sEH-mediated metabolism of fatty acids

The sEH enzyme, which is encoded by *Ephx2* gene, plays an important role in eicosanoid metabolism [26]. It catalyzes hydrolysis of fatty acid epoxides, which are produced from polyunsaturated fatty acids by the actions of cytochrome P450 (CYP) monooxygenases, to generate the corresponding fatty acid diols (Figure 1). The fatty acid epoxides are important lipid signaling molecules that have potent biological actions such as anti-inflammatory, cardio-protective, tissue-protective, and pro-angiogenic effects; in contrast, the fatty acid diols are usually less active or even pro-inflammatory [26-29]. Therefore, the metabolic activity of sEH leads to reduced concentrations of potentially beneficial metabolites (fatty acid epoxides) and/or increased concentrations of potentially inactive or harmful metabolites

(fatty acid diols). Substantial research has shown that sEH plays critical roles in the pathogenesis of many diseases, including inflammation, hypertension, pain, and angiogenesis [26]. The pharmacological inhibitors of sEH are being evaluated in multiple human clinical trials [24, 25]. Notably, GlaxoSmithKline is conducting human clinical trials to test the effect of a sEH inhibitor and has shown that the drug candidate is safe, well-tolerated, and causes sustained inhibition of sEH in humans [24]. In addition, other classes of sEH inhibitors are being considered for human trials [25].

2. Changes of the sEH pathway in obesity

Our recent research showed that the expression of sEH and the concentrations of sEH-produced fatty acid diols are increased in the colon tissues of diet-induced obese mice [7]. We treated C57BL/6 mice with a control diet (low-fat diet) (10 kcal% from fat, catalog # D12450J from Research Diets Inc., this diet mimics a normal rodent diet which has a similar level of fat) or a high-fat diet (HFD) (60 kcal% from fat, catalog # D12492) for 8 weeks. These diets are among the most widely-used diets for obesity research (see our publications [7, 20, 30, 31] and others [32]). LC-MS/MS analysis showed that the concentrations of sEH-produced fatty acid diols, including arachidonic acid (ARA)-derived 8,9-, 11,12-, and 14,15-dihydroxyeicosatrienoic acid (DHET), eicosapentaenoic acid (EPA)-derived 17,18-dihydroxyeicosatetraenoic acid (DiHETE), and docosahexaenoic acid (DHA)-derived 7,8-, 10,11-, 16,17-, and 19,20-dihydroxydocosapentaenoic acid (DiHDPE) (see chemical structures of these metabolites in Figure 1), were significantly increased in the colon tissues of HFD-induced obese mice. Next, we analyzed expressions of proteins involved in biosynthesis of fatty acid diols, and found that the transcriptional and protein expression levels of sEH were increased in the colon tissues of HFD-induced obese mice. In contrast, other proteins, such as *Pla2g4a* (encoding cytosolic calcium-dependent PLA_2) or *Cyp monooxygenases* were not changed [7]. Overall, these results showed that the sEH pathway is upregulated in the colon tissues of diet-induced obese mice.

Our result is well in agreement with previous studies which showed that the sEH pathway is upregulated in animal models of obesity. The expression and/or activity of sEH was increased in many tissues, such as adipose [33, 34], liver [8, 9, 34], and kidney [10], of HFD-induced obese mice. Furthermore, previous studies also support the hypothesis that sEH is upregulated in genetically induced obese animals. Zucker rat is a widely-used animal model of genetic obesity [35]. Zhao et. al showed that compared with lean Zucker rats, the expression of sEH in mesenteric artery is increased in obese Zucker rats [36]. There are also inconsistent results, which showed that the expression of sEH is not altered in left ventricular tissue of diet-induced obese mice [37] or renal cortical tissue of obese Zucker rats [38], suggesting that the sEH pathway could be upregulated in obesity in a tissue-specific manner.

Human studies support the hypothesis that the sEH pathway is upregulated in obese individuals, though there are inconsistent results. Theken *et al.* showed that compared with non-obese atherosclerotic cardiovascular disease (CAD) patients, the obese CAD patients have reduced concentrations of EETs (substrates of sEH), as well as a lower ratio of 14,15-EET (a substrate of sEH) to 14,15-DHET (a product of sEH), in the plasma [39]. This result

supports that the sEH pathway is upregulated in obese individuals. We need to point out that there are inconsistent results from human studies. For example, Pickens *et al.* showed that compared with lean individuals, the plasma concentrations of sEH-produced fatty acid diols were decreased in the plasma of obese individuals [40]. There could be many reasons for these inconsistent results in human studies. In most human studies, only the concentrations of eicosanoids in the circulation were measured [39, 40]. Our previous studies showed that the circulating concentrations of many eicosanoids, including sEH-produced fatty acid diols, were not significantly changed in HFD-induced obese mice [31], though their concentrations were altered in the colon tissues of obese mice [7]. These findings suggest that the circulating eicosanoids could be poor predictors of metabolic changes induced by obesity.

3. Roles of sEH in mediating obesity-induced disorders

Previous studies have shown that genetic ablation or pharmacological inhibition of sEH doesn't have a major impact on obesity (e.g. body weight), but attenuates the development of a wide range obesity-induced disorders, including endoplasmic reticulum (ER) stress, metabolic syndrome, insulin resistance, fatty liver, hepatic steatosis, inflammation, and endothelial dysfunction [11-19]. Overall, these results support the hypothesis that sEH plays an important role in the pathogenesis of various obesity-induced disorders. The details are discussed below.

3.1 Roles of sEH in obesity-induced colonic inflammation and associated disorders

Obesity is associated with enhanced colonic inflammation [41-43], which is a major risk factor of developing CRC [44]. CRC is the third most common cancer and the second leading cause of cancer-related death in the United States [4]. Every year there are ~130,000 new cases and ~50,000 fatalities from CRC in the United States [4]. It is well established that obese individuals have higher risks of developing CRC and late-stage CRC [5, 45]. Considering the obesity epidemic and the potential lethal consequence of CRC, obesity-enhanced CRC is a serious health problem in the United States. However, the mechanism by which obesity increases the risks of CRC is not well understood [6].

Our recent research shows that the sEH pathway is upregulated in the colon tissues of diet-induced obese mice; in addition, inhibition or genetic ablation of sEH abolishes obesity-induced colonic inflammation and activation of pro-tumorigenic Wnt signaling [7]. Specifically, our research shows that: (*1*) the expression of sEH and the concentrations of sEH-produced metabolic products (fatty acid diols) are increased in the colon tissues of diet-induced obese mice; (*2*) inhibition or genetic ablation of sEH attenuates obesity-induced colonic inflammation, with reduced expression of pro-inflammatory cytokines and decreased infiltration of immune cells in colon; and (*3*) inhibition or genetic ablation of sEH attenuates obesity-induced activation of pro-tumorigenic Wnt signaling in colon, as indicated by reduced phosphorylation of GSK3β and decreased expression of *Axin2* in colon [7]. Together, these results demonstrate that sEH is important for the pathogenesis of obesity-induced colonic inflammation. Notably, we found that oral administration of two different sEH inhibitors (via drinking water), at low doses, abolished obesity-induced colonic inflammation and activation of Wnt signaling [7], supporting that the sEH inhibitors could

potentially be novel agents for preventing or treating obesity-induced gut inflammation and its associated disorders. In our experiments, we performed the studies using male mice, further studies are needed to determine the extent to which genetic ablation or inhibition of sEH attenuates obesity-induced colonic inflammation in a sex-dependent manner.

Previous research suggests that it is feasible to target sEH to reduce the risks of colonic inflammation and colon cancer. Two previous studies have shown that compared with normal colon tissues, the expression of sEH is increased in human CRC samples [46, 47], supporting the notion that sEH could be a therapeutic target of CRC. Furthermore, inhibition or genetic ablation of sEH attenuates the development of dextran sodium sulfate (DSS)- or IL-10-deficiency-induced colitis and CRC [47-49]. Together with our finding [7], these results support that sEH could be a novel therapeutic target for obesity-associated CRC. A recent human study showed that obesity significantly increased the risks of developing CRC in patients with Lynch syndrome (LS, an inherited genetic condition that increases risks of developing certain cancers such as CRC), while this risk is abrogated in those taking aspirin [50]. This result supports that targeting inflammation, or more specifically eicosanoid signaling in inflammation, is a promising approach to reduce the risk of obesity-associated CRC. Further studies are needed to determine the roles of sEH-mediated eicosanoid signaling pathway in obesity-associated CRC.

3.2 Roles of sEH in obesity-induced nonalcoholic fatty liver disease (NAFLD)

NAFLD, characterized by an extra accumulation of fat in liver tissues, affects 80-100 million Americans [51]. Obesity is a major risk factor of developing NAFLD, and 30-90% of NAFLD patients are obese [52]. Animal studies support that it is feasible to target sEH to reduce the risks of obesity-induced NAFLD. Schuck et al. showed that compared with the mice fed with standard chow (14 Cal% from fat), mice treated with an atherogenic diet (40 Cal% from fat) developed NAFLD, with exaggerated systematic and hepatic inflammation, and hepatic injury. These effects were significantly attenuated in the sEH KO mice, illustrating a critical role of sEH in regulating obesity-induced NAFLD [53]. Furthermore, genetic ablation of sEH increased concentrations of EETs, as well as the EET-to-DHET ratio, in both the plasma and liver of the atherogenic diet-treated mice, supporting the involvement of sEH-mediated lipid signaling pathway [53]. Consistent with this study, other studies have also shown that genetic ablation or pharmacological inhibition of sEH, or overexpression of CYP monooxygenases, attenuates obesity-induced hepatic inflammation, ER stress and hepatic steatosis [8, 9, 34, 54, 55], demonstrating an important role of the sEH pathway in the pathogenesis of obesity-induced NAFLD.

3.3 Roles of sEH in obesity-induced Type 2 diabetes

Type 2 diabetes, which is the most common type of diabetes, is characterized by an abnormally high concentration of glucose in bloodstream [56]. Obesity is a major risk factor in developing type II diabetes [56, 57]. Recent research supports that inhibition or genetic ablation of sEH attenuates obesity-induced type 2 diabetes. Luria et al. showed that HFD treatment caused insulin resistance and glucose intolerance in mice, while such effects were significantly attenuated by genetic ablation or pharmacological inhibition of sEH, resulting in lower concentrations of plasma glucose and improved insulin tolerance in mice [58].

Interestingly, inhibition of sEH did not reduce the concentration of blood glucose in non-obese mice (fed with standard chow), while reduced blood glucose in obese mice (fed with HFD) [58]. Consistent with ith this study, other studies have also shown a beneficial effect of targeting sEH in animal models of obesity-induced type 2 diabetes [59-61].

3.4 Roles of sEH in obesity-induced kidney diseases

Obesity is also a critical risk factor for developing chronic kidney diseases [62]. Huang et al. showed that treatment with a sEH inhibitor reduced mean arterial pressure, renal vascular resistance, cumulative sodium balance, and glomerular filtration rate, while increased renal blood flow in HFD-treated rats, demonstrating that inhibition of sEH attenuates obesity-induced abnormal renal function [63]. Roche et al. showed that in HFD-induced obese mice, inhibition of sEH attenuates the development of renal dysfunction, and reduced renal inflammation with reduced activation of NF-κB pathway and decreased renal expression of MCP-1, VCAM-1 and COX-2 [64]. In agreement with these two studies, others have also shown that inhibition of sEH attenuates the development of obesity-induced kidney disorders [10, 65].

4. Intestinal barrier function plays an important role in mediating obesity-induced disorders

The exact mechanisms by which obesity increases risks of a wide range of diseases are not fully understood. Recent research supports that obesity-induced intestinal barrier dysfunction could play a central role in mediating various obesity-induced disorders [66-69]. Indeed, previous research has shown that obese subjects have compromised intestinal barrier function, and this leads to translocation of bacteria or toxic bacterial products from the gut into the bloodstream and distant organs, resulting in systemic inflammation, insulin resistance, and tissue dysfunction [66-69].

Animal studies support that obesity induces intestinal barrier dysfunction and enhances bacteria translocation. Cani et al. showed that compared with mice fed with a normal diet, the HFD-induced obese mice had impaired expression of tight-junction proteins in the colon, increased gut leakage (as assessed by a FITC-dextran permeability assay), and higher concentrations of lipopolysaccharide (LPS) in the circulation, illustrating intestinal barrier dysfunction in the diet-induced obese mice [66, 68]. Furthermore, Cani et al. showed that HFD-induced intestinal barrier dysfunction through gut microbiota-dependent mechanisms, since antibiotic cocktail-mediated suppression of gut bacteria attenuates the effects of HFD on gut leakage [68]. Besides diet-induced obesity, previous studies have also shown that genetically obese (*db/db*) mice had reduced expression of tight-junction protein in the colon, enhanced gut leakage (as assessed by using FITC-dextran- and *Citrobacter rodentium*-based permeability assays), and higher concentrations of microbial pattern recognition receptor (PRR) ligands in serum, spleen, and liver, demonstrating impaired intestinal barrier function and enhanced bacterial translocation in the *db/db* mice [21]. In agreement with these studies, other studies have shown that diet- or genetically induced obese mice develop intestinal barrier dysfunction [70-74].

Human studies also support the hypothesis that obese individuals have impaired intestinal barrier function, though there are inconsistent results [69]. Consistent with the results from the aforementioned animal studies [66, 68], Pendyala et al. showed that a 1-month treatment with Western-style diet (high fat diet) in healthy subjects induced a ~70% increase of the plasma concentration of LPS, while a prudent-style diet (with similar caloric density as Western-style diet but with less fat and more carbohydrates and fiber) reduced LPS by ~30% [75]. Furthermore, Erridge et al. showed that intake of HFD can induce a rapid increase of plasma concentration of LPS in human subjects: 4 hours after initiation of HFD intake, the plasma concentration of LPS was increased by ~50% [76]. Besides HFD, other human studies also support that the circulating concentration of LPS is increased in obese subjects. Basu et al. showed that the plasma concentrations of LPS in lean versus obese pregnant women were 0.5 ± 0.2 EU/mL versus 1.0 ± 0.5 EU/mL (P = 0.006), supporting that obesity induces intestinal barrier function in pregnant women [77]. A similar result was also observed in other studies [78-80].

Accumulating evidence supports the hypothesis that obesity-induced intestinal barrier dysfunction and its resulted bacterial translocation could play a central role in mediating various obesity-induced disorders [66]. The presence of gut bacteria is essentially required for the development of obesity-induced disorders. Treatment with antibiotic, which depletes bacteria and bacterial products, attenuated HFD-induced adipose inflammation and dysfunction, and insulin resistance in mice [68]. Compared with conventionally raised mice, HFD-induced obesity, insulin resistance, hepatic steatosis, and dyslipidemia were attenuated in germ-free mice [81, 82]. Furthermore, recent studies support that continuous infusion with low, non-toxic dose LPS, which mimics HFD-induced elevation of bacteria/LPS translocation, can cause disorders that are similar to those induced by obesity. Cani et al. showed that continuous infusion with 300 μg/kg/day LPS via mini-pumps increased plasma concentration of glucose and insulin, increased body weight, enlarged liver and adipose tissues, and exaggerated fat accumulation in liver tissues in non-obese mice [66]. Dapito et al. also showed that infusion with 300 μg/kg/day LPS exaggerated diethylnitrosamine (DEN)/carbon tetrachloride (CCl_4)-induced hepatocellular carcinoma, with increased tumor number and tumor size [83]. Overall, these results support a potential role of the intestinal barrier dysfunction-induced bacteria/LPS translocation in promoting obesity-associated disorders.

5. Roles of sEH in regulating obesity-induced intestinal barrier dysfunction and its resulting pathologies

The molecular mechanisms by which obesity induces barrier dysfunction remain poorly understood, and represent a significant knowledge gap [84, 85]. Our recent research supports that sEH is a novel endogenous regulator of obesity-induced intestinal barrier dysfunction and its resulted disorders, via gut microbiota-dependent mechanisms [20]. Compared with control mice (maintained on a low-fat diet), HFD-induced obese mice had compromised intestinal barrier function (as assessed by a FITC-dextran permeability assay), a higher concentration of LPS in the plasma, and higher amount of bacterial DNA in the bloodstream and adipose tissue. These results illustrate exaggerated gut leakage and enhanced bacterial

translocation in the obese mice, which are consistent with previous studies [21, 66-69, 75-77, 86]. Genetic ablation of sEH abolished such effects in the obese mice, supporting a critical role of sEH in mediating obesity-induced intestinal barrier dysfunction. Furthermore, we showed that genetic ablation of sEH altered obesity-associated gut microbiota and the detrimental actions of sEH on intestinal barrier function were abolished by antibiotic cocktail-mediated suppression of the microbiota. Indeed, without the antibiotic treatment, genetic ablation of sEH attenuated HFD-induced gut leakage and bacterial translocation; while with the antibiotic treatment, genetic ablation of sEH had no such effects [20]. This finding supports a critical role of the microbiota in mediating the activities of sEH on the barrier function. If further validated, this represents a new mechanism for the biological functions of sEH, since very little is known about the effect of sEH-mediated lipid signaling on gut microbiota and its connection to human diseases.

We found that sEH-produced lipid metabolites play critical roles in mediating the barrier-disrupting effects of sEH, further supporting sEH as a critical regulator of intestinal barrier function. Treatment with dihydroxyeicosatrienoic acids (DHETs, derived from ω-6 ARA), using mini-pumps, induced gut leakage, impaired colonic expression of a tight-junction protein Claudin-5, and enhanced colonic expression of pro-inflammatory cytokines, in mice. These results suggest that sEH-produced lipid metabolites have potent actions on inducing intestinal barrier dysfunction and colonic inflammation *in vivo*, further supporting a critical role of sEH in driving gut disorders [20]. This finding is interesting since most previous studies have suggested that the sEH-derived fatty acid diols are biologically inactive [26]. Previous studies showed that ω-3 versus ω-6 polyunsaturated fatty acids have opposite effects on intestinal barrier function [87], it is feasible that ω-3 versus ω-6 fatty acid diols could have different actions on barrier function and more studies are needed to determine the actions of individual sEH-produced fatty acid diols.

To date, there are few therapeutic strategies for preventing or treating intestinal barrier dysfunction and its resulting disorders. Our results support that pharmacological inhibitors of sEH could be promising agents for preventing or treating obesity-induced intestinal barrier dysfunction and its resulted disorders. Oral administration of a sEH inhibitor *t*-TUCB (administered via dissolving in drinking water), at a low dose (~ 1mg/kg/day), abolished HFD-induced colonic inflammation, intestinal barrier dysfunction, bacterial translocation, as well as bacterial invasion-induced adipose inflammation and dysfunction. Regarding the mechanisms by which the sEH inhibitor attenuates barrier dysfunction, we found that compared with control mice (maintained on a low-fat diet), the HFD-induced obese mice had lower expression of tight-junction proteins in the colon, while such effects were abolished by treatment with the sEH inhibitor [20]. This finding could be clinically important because the sEH inhibitors have been evaluated in multiple human clinical trials targeting other chronic disorders [24, 25].

6. Future work

Overall, previous studies from us and others support that sEH could be an important therapeutic target for preventing and/or treating a wide range of obesity-induced chronic disorders, at least in part through attenuating obesity-induced intestinal barrier dysfunction

[7, 11-20]. A better understanding of the molecular mechanisms by which sEH regulates intestinal barrier function could be important for clinical applications of sEH inhibitors, as well as development of novel therapeutic targets for obesity-induced disorders. We have shown that treatment with sEH-derived metabolites, DHETs, caused colonic inflammation and gut leakage in mice, supporting a critical role of sEH metabolites in mediating the actions of sEH on barrier function [20]. Many eicosanoids act by binding to specific G-protein coupled receptors (GPCRs) [88]. Emerging research support that CYP/sEH-derived eicosanoids, such as EETs, also act via GPCR-dependent mechanisms, though the specific receptor(s) remain to be elucidated and validated [89-91]. It would also be important to discover the direct cellular targets or receptors of the sEH metabolites such as DHETs, since the identified proteins could serve as novel therapeutic targets of barrier dysfunction, and therefore have important implications in the pathogenesis of many human diseases. In addition, based on the potent actions of DHETs, the sEH-derived metabolites could be potential structural targets to develop stable antagonists that counteract their actions and serve as novel therapeutics to treat barrier dysfunction. Recent studies support that it is feasible to design synthetic mimics of CYP/sEH-derived metabolites as potential therapeutic drugs [92-95]. The elucidation of the direct cellular targets or receptors of the sEH metabolites could further help the rational design of synthetic mimics and facilitate drug discovery and development.

Besides obesity-related disorders, intestinal barrier dysfunction has also been shown as a key and direct pathogenic factor of many other human diseases, including infectious diseases [96-99], inflammatory bowel disease [100], aging [101], sepsis [102-104], and diabetes [85, 105]. It is important to determine the potential role of sEH in the development of other diseases and the roles of barrier function involved.

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Highlights

- Soluble epoxide hydrolase (sEH), an important enzyme involved in fatty acid metabolism, is upregulated in many tissues of obese animals.
- Substantial studies have shown that genetic ablation or pharmacological inhibition of sEH attenuates the development of a wide range of obesity-induced disorders.
- Our recent research has shown that genetic ablation or inhibition of sEH attenuates obesity-induced intestinal barrier dysfunction and its resulted bacterial translocation, which is widely regarded to be a central mechanism for the pathogenesis of various obesity-induced disorders.

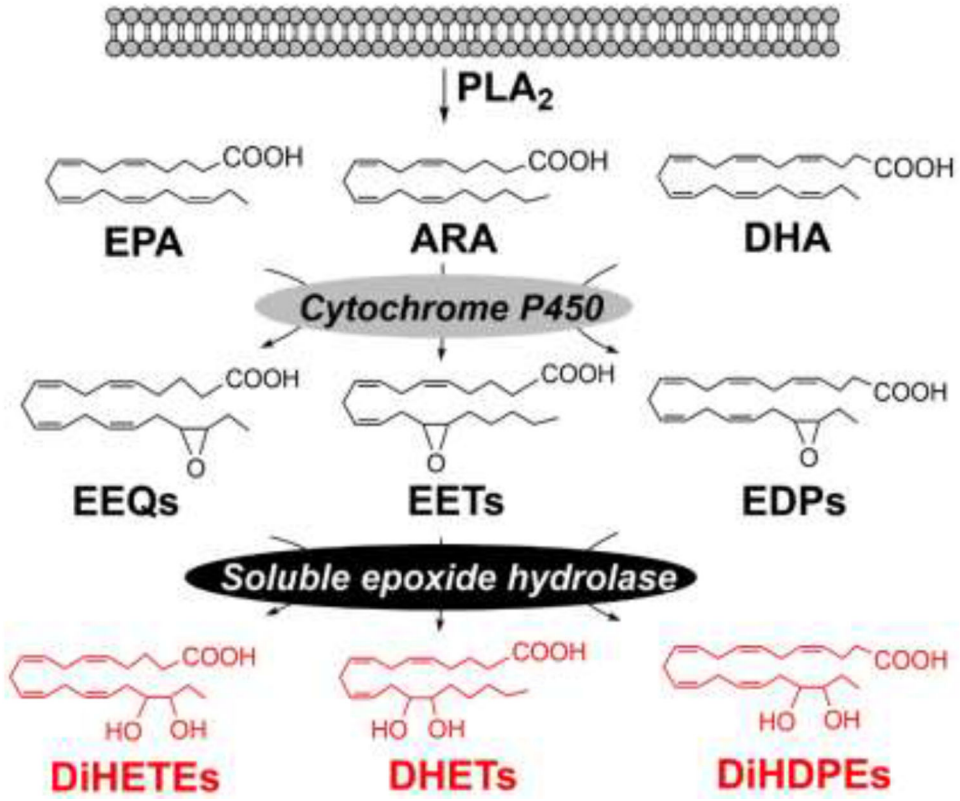

Figure. 1. Biochemistry of sEH-mediated metabolism of fatty acids:
sEH catalyzes hydrolysis of fatty acid epoxides to the corresponding fatty acid diols.

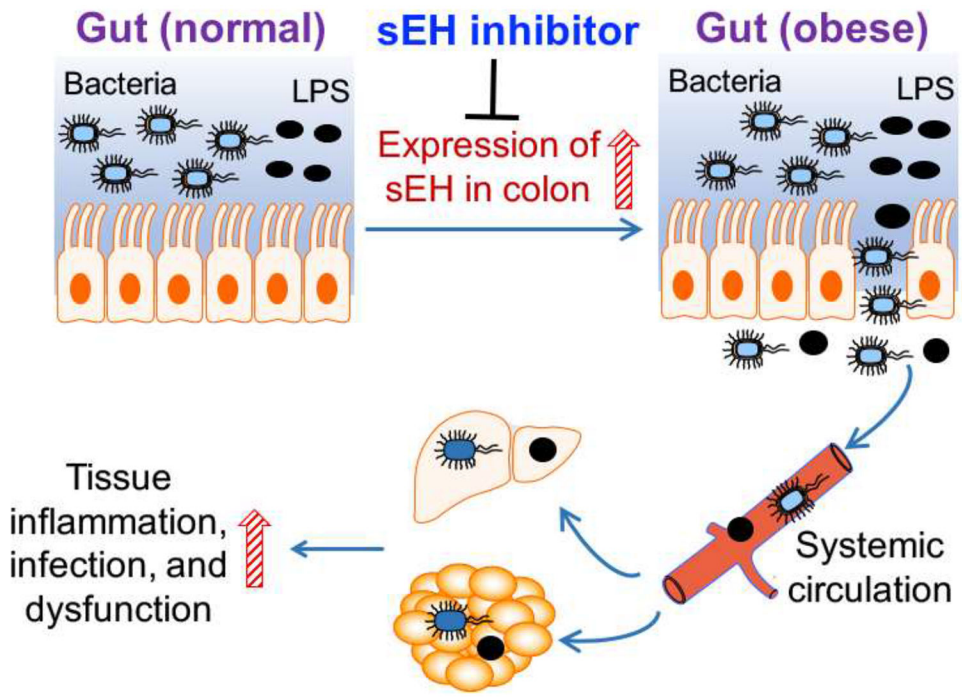

Figure 2.

sEH is a novel endogenous regulator of obesity-induced intestinal barrier dysfunction. Genetic ablation or inhibition of sEH could attenuate various obesity-induced disorders, through inhibiting obesity-induced intestinal barrier dysfunction.