Chapter 2

Current Pharmacotherapies for NASH
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The major goal of NASH treatment is to improve hepatic steatosis, inflammation and prevent the development of fibrosis, cirrhosis and end stage liver disease. At present, weight loss has been suggested as a first line therapy for the treatment of NASH patients through calorie restricted diet or regular physical exercise. It has been reported that 7-9% of weight loss reduces hepatic steatosis, hepatocyte ballooning and hepatic inflammation in NASH patients [1]. However, maintaining long term weight loss through calorie restriction is very difficult. Consequently, several pharmacotherapies have been studied with the aim of improving insulin sensitivity and reducing the pro-inflammatory mediators potentially involved in the progression of NASH. Most of the therapeutic classes such as statins, fibrates, antioxidants, insulin sensitizers and angiotensin receptor blockers were used in the management of NASH/NAFLD patients. Unfortunately, all of these treatments demonstrated modest or variable efficacy in randomized clinical trials [2, 3]. Notably, Pioglitazone or Vitamin E can be recommended for the treatment of NASH patients who failed lifestyle intervention. In the Phase III PIVENS trial [4], pioglitazone demonstrated a trend in improvement of histology (a secondary endpoint) as compared to placebo (34% vs. 19% p = 0.04) and Vitamin E also showed histological improvement (Vitamin E vs placebo: 43% vs. 19%, p < 0.001). However, pioglitazone failed to meet the primary endpoint i.e. histological improvements although it demonstrated improvement in hepatic injury markers, steatosis and inflammation in nondiabetic NASH patients treated for 96 weeks. But, long term use of pioglitazone raises concerns like increased bone loss, weight gain, bladder cancer and congestive heart failure which may limit its use in the treatment of NASH patients [5]. There are concerns about the long-term effects of Vitamin E also such as increased risk of
hemorrhagic stroke or prostate cancer and increase in all-cause mortality with high
dose treatment in NASH patients [1]. Moreover, newer pharmacological treatments
such as Farnesoid X Receptor (FXR) agonist, Obeticholic acid, Elafibranor (GFT505,
PPARα/δ agonist) and Saroglitazar (PPARα/γ agonist) have demonstrated modest
beneficial effects in liver histology in NASH patients and Phase III trials are ongoing
for confirming their safety and efficacy [3]. Recently, the role of newer anti-diabetes
drugs such as GLP-1 receptor agonists and DPPIV inhibitors has been suggested in
the treatment of NASH [6]. Due to multifactorial pathogenic pathways involved in the
progression of NASH, it has been suggested that combination therapies will likely
provide greater success in future. The pharmacological actions of incretin based
therapies, fibrates and GPR119 agonists are listed below. Based on the available
information, we investigated effect of anti-diabetic drug, APD668, a GPR119 agonist
alone or in combination with linagliptin, a DPPIV inhibitor or fenofibrate, a PPAR-α
agonist, in murine models of NASH.

2.1 Incretin Based Therapies

Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone secreted by
the small intestine in response to nutrient ingestion. It has been reported that GLP-1
improved glucose homeostasis via glucose-dependent insulin secretion and reduced
postprandial glucagon secretion in diabetic patients. Moreover, pleiotropic effects of
GLP-1 includes weight loss, decreased feed intake, inhibition of gastric emptying,
 improvement in insulin sensitivity and lowering of postprandial lipids levels [7-9].
Once secreted, GLP-1 is quickly degraded by Dipeptidyl Peptidase IV (DPPIV). As,
DPPIV inhibitors prolong the activity of GLP-1, they have been used for the treatment
of diabetes patients. Recently, incretin-mimetics have generated greater interest
because of their potential to reduce hepatic steatosis and hepatic injury markers in
NAFLD patients [6]. Therefore, GLP-1R agonists and DPPIV inhibitors have been proposed in the management of NASH/NAFLD patients.

2.1.1 Glucagon-like peptide-1 (GLP-1) Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists such as Exenatide and Liraglutide has been approved for the treatment of diabetic patients. Previously, it has been reported that Exendin-4 reduced hepatic steatosis by modulation of lipid metabolism and improving hepatic insulin sensitivity in ob/ob mice [10, 11]. AC3174 (analogue of exenatide) also demonstrated significant reduction in body weight, fat mass, biochemical markers (ALT, TG, TC and PG), hepatic steatosis and fibrosis marker i.e. collagen-1 protein by histology and quantitatively in high trans-fat (HTF) diet induced steatohepatitis model [12]. Moreover, Liraglutide ameliorated hepatic steatosis, liver enzyme markers, fibrosis and hepatocarcinogenesis in murine models of NASH [13, 14]. Both Exenatide and Liraglutide demonstrated significant improvement in fasting glucose, triglyceride, liver enzymes, liver inflammation and fibrosis in NAFLD diabetic patients [15]. However, the exact mechanism through which GLP-1R agonist cause improvement in NASH is not known. It has been suggested that GLP-1R agonist caused (direct action) impairment in hepatocyte de novo lipogenesis and/or enhance β-oxidation of fatty acids through GLP-1 receptors present in hepatocytes or indirectly through appetite suppression and weight reduction probably leading to improvement in insulin sensitivity in NASH patients [10, 11, 16].

2.1.2 Dipeptidyl Peptidase IV (DPPIV) Inhibitors

DPPIV inhibitors may also have potential for the treatment of NASH because patients with NASH have increased DPPIV activity which correlates with histological severity [17, 18]. DPPIV inhibitors such as Sitagliptin and Linagliptin demonstrated significant improvement in steatosis, liver enzymes, lipid levels, oxidative stress,
inflammation and fibrosis markers in rodent studies [19-23]. Furthermore, Sitagliptin and Vildagliptin showed improvement in hepatic injury markers and hepatic steatosis in NAFLD diabetic patients [24, 25]. Recently, Alogliptin was also shown reduced NAFIC score (NASH, ferritin, insulin, type 4 collagen 7S) in NASH patients [26]. However, all these RCTs have limitations and show conflicting results because the final conclusion has been drawn from a small patient cohort. In addition, DPPIV inhibitors did not show significant improvement in inflammation and fibrosis in NASH patients. It has been proposed that DPPIV inhibitors demonstrated improvement in steatohepatitis either via preventing degradation of GLP-1 levels or through inhibiting genes related to lipogenesis in NASH patients [3, 15, 27]. Therefore, further studies are needed to fully confirm anti-NASH efficacy of these agents in clinical trials.

2.2 Anti-dyslipidemic Agents

Previously, it has been reported that dyslipidemia predominantly hypertriglyceridemia and insulin resistance plays a significant role in the pathogenesis of NASH. Various anti-dyslipidemic drugs such as statins (mainly Atorvastatin), fibrates (Fenofibrate, Bezafibrate) and Ezetimibe (inhibitors of NPC1L1) have been tried for the treatment of NASH [2].

2.2.1 Fibrates

Fibrates are the first line of therapy for treatment of dyslipidemic patients. Fibrates acts through activation of Peroxisome Proliferator Activated Receptors (particularly PPAR-α) involved in lipid and glucose metabolic pathways. PPAR-α is predominantly expressed in liver (hepatocytes), adipose tissue, skeletal muscle and intestine. Fenofibrate is one of the most widely used fibrates. Several published reports suggest that PPAR-α agonists showed improvement in liver enzymes,
steatosis, inflammation and fibrosis in murine models of NASH [28-30]. This benefit can be attributed to its anti-dyslipidemic, anti-oxidant and anti-inflammatory activity in NASH models [31]. Clinical studies also reported that fibrate therapy provides benefit in NASH patients by improving liver enzyme markers, steatosis and inflammation, although liver histology did not change significantly compared to the placebo group. However, this benefit needs to be assessed further in large randomized clinical trials [31, 32].

2.3 GPR119: A Novel Therapeutic Target for NASH

Type 2 diabetes is a chronic metabolic disorder characterized by high glucose levels, insulin resistance and a reduced function of β-cell over time. Several anti-diabetes therapies are available in the market but suffer from inadequate efficacies and tolerability, along with marked mechanism-related side effects such as hypoglycemia, weight gain, bone loss and gastrointestinal problems [33]. Recently, GPR119 modulators have been suggested for the treatment of metabolic disorders.

2.3.1 GPR119: Discovery and Receptor Expression

The G protein-coupled receptor 119 (GPR119) was first identified through a bioinformatics approach and has been described as a rhodopsin-like, class A receptor [34]. The human GPR119 gene is located on the X chromosome (Xp26.1) and contains 335 amino acid residues. This receptor has been described in the literature under various synonyms, including SNORF25 [35], RUP3 [36], GPCR2 [37], 19AJ [38], OSGPR116 [39] and glucose-dependent insulinotropic receptor [40, 41]. Based on phylogenetic analysis and sequence similarity, GPR119 belongs to the biogenic amine and MECA (Melanocortin, Endothelial differentiation gene, Cannabinoid, and Adenosine) receptor clusters. However, GPR119 shares 28% transmembrane sequence homology with Adenosine A1 and A3 receptors whereas it does not have
significant sequence similarity to GPR40/FFAR1 (18%) and GPR120/FFAR4 receptors (24%) [42]. Mo XL et al. [43] revealed that the mouse GPR119 shares 82.1% homology and rat GPR119 shares 73.7% homology with human GPR119. Several groups have investigated the GPR119 receptor expressions using RT PCR or hybridization analysis. GPR119 receptors were predominantly expressed in β-cells of pancreas and entero-endocrine (L and K) cells of intestinal [40, 44, 45]. However, relatively low expression GPR119 receptor has been found in brain, liver and skeletal muscle [41, 46-48]. Interestingly, Gpr119 mRNA level in human fetal liver is very high [49]. Recently, Yang JW et al. [50] for the first time revealed that GPR119 receptors were expressed in mouse hepatocytes and liver tissues. However, the expression of GPR119 in adipose tissues is unknown at present.

2.3.2 GPR119: Signaling and Physiological Functions

GPR119 is a rhodopsin-like, class A receptor. It has been demonstrated that GPR119 receptors predominantly couple through Gαs/cAMP pathway and lead to stimulation of adenylate cyclase [35, 40]. Many endogenous ligands and synthetic small molecule agonists of GPR119 have been shown to increase cAMP levels. The fatty acid derivatives such as lysophosphatidylcholine (LPC), oleylethanolamide (OEA), N-oleolydopamine (OLDA) and 2-oleoylglycerol (2-OG) have been reported as an endogenous ligands of GPR119 [46, 47, 51, 52]. In in-vitro studies, these endogenous ligands were demonstrated to increase cAMP, enhanced glucose stimulated insulin secretion and also GLP-secretion via GPR119 receptor [44, 46, 47, 51]. Notably, OLDA also improved glucose tolerance with increased GIP levels in GPR119 wild-type but not in knockout mice [51]. Overall, GPR119 agonists acts via a dual mechanism of action 1) activation of GPR119 receptor in pancreatic β cells results in direct stimulation of glucose-dependent insulin secretion 2) activation of
GPR119 in entero-endocrine cells results in stimulation of incretin release (GLP-1 & GIP), leading to improved acute glucose tolerance. However, GPR119<sup>+/−</sup> mice have normal islet function, body weight, and fed/fasted glucose levels [40, 41]. Moreover, there were no significant differences in body weight gain, glucose levels and insulin sensitivity when GPR119<sup>+/−</sup> and GPR119<sup>−/−</sup> mice fed on high fat diet [53]. But, GLP-1 secretion was significantly attenuated in GPR119<sup>−/−</sup> mice as compared to wild-type mice, suggesting that GPR119 receptors play a major role in the regulation of GLP-1 secretion [53, 54].

2.3.3 GPR119 Agonists: Preclinical Pharmacology

GPR119 receptor agonists caused increase in intracellular cAMP levels in pancreatic β-cells and further potentiated glucose-stimulated insulin secretion (GSIS) in preclinical studies. Several GPR119 agonists have shown enhanced insulin and incretin secretion, improved glucose tolerance, inhibition of gastric emptying, suppression of feed intake, and finally body weight loss in rodent studies [55]. The pharmacological actions of GPR119 receptor agonists are depicted in Figure 2.3.3.

**Figure 2.3.3 Pharmacological actions of GPR119 agonist**, Ref: Dhayal S and Morgan NG. 2010 [55].
2.3.4 GPR119 Agonists: Anti-diabetes Therapy

Arena Pharmaceuticals demonstrated that AR231453, a first generation GPR119 agonist improved oral glucose tolerance, increased GSIS and also enhanced GLP-1, GIP and total PYY release in mice [41, 42]. The authors also revealed that the AR231453 showed partial improvement in glucose tolerance in presence of exendin-3 (GLP-1R antagonist) suggesting that indirect actions via GLP-1 release and also direct actions on pancreatic β-cells contribute to glucose homeostasis. Sub-chronic treatment with APD668, a second generation compound also demonstrated significant blood glucose and HbA1c reduction in male ZDF rats [56]. Additionally, a third generation compound, APD597 (INJ-38431055) which was co-developed by Arena and Johnson & Johnson also showed significant improvement in Lep<sup>ob/ob</sup> mice, ZDF rats and monkeys [57]. CymaBay Therapeutics (formerly Metabolex) developed MBX2982, a potent and specific GPR119 agonist that increased incretin levels, GSIS, improved glucose tolerance and delayed the onset of diabetes in high fat diet fed female ZDF rats [58]. Another, GPR119 agonist, GSK1292263 reduced HbA1c and glycemic excursion in ZDF rats [59]. Furthermore, PSN632408 (Prosidion), AS1669058 (Astellas Pharma Inc.), BMS-903452 (Bristol Myers Sqibb), HD0471953 (Hyundai Pharmaceutical Co. Ltd), YH18421 (Yuhan R&D Institute, Korea) also caused significant improvement in glucose tolerance and insulin secretion in rodent studies [47, 60-63]. Some of the GPR119 agonists such as AR231453, MBX2982 and YH18421 have shown significant additive glucose lowering efficacy and synergistically enhanced GLP-1 levels in rodent studies [41, 58, 63]. Furthermore, AR231453 and AS-1265974 stimulated β-cell replication and GLP-1 secretion in streptozotocin induced diabetic mice [64, 65]. Similarly, PSN632408, a GPR119 agonist alone or in combination with sitagliptin, a DPPIV inhibitor increased human
β-cell neogenesis in human-islet-transplanted NOD-SCID mice [66, 67]. Recently, another GPR119 agonist, DA-1241 also demonstrated significant preservation of β-cells mass in HFD/STZ diabetic mice model [68]. Overall, these finding suggest that GPR119 agonists improved glucose excursion via direct action on pancreatic β-cells and indirect action via incretin release partially thus contributing to improvement in glucose tolerance and the preservation of β-cells in rodent studies.

2.3.5 GPR119 Agonists: Anti-obesity Therapy

Oleylethanolamide (OEA) an endogenous ligand of GPR119 and GLP-1 whose secretion was increased by GPR119 agonist, both demonstrated reduction in feed intake in rodents [69, 70]. Therefore, it is tempting to speculate that GPR119 agonists might have role in appetite suppression, gastric emptying and body weight loss. However, Fu J et al. [71] proposed that the actions of OEA could be due to activation of PPAR-α receptor and the effect on feed intake was independent of GPR119 because OEA also showed effect in both GPR119 wild-type and knockout mice [53]. It is very well known that GPR119 agonists stimulated GLP-1 secretion, caused inhibition of gastric emptying and appetite suppression leading to body weight loss in preclinical and clinical studies [72, 73]. Based on this rationale, oral administration of PSN821 showed reduced weight gain (8.8%), fat pad weight and plasma leptin levels in diet-induced obese rats. PSN821 also caused inhibition of gastric emptying in normal rats [47, 74]. Importantly, Chu ZL et al. [41] did not observe any effect on feed intake or body weight in their studies; rather compounds more potent than AR231453 showed feed intake reductions only at higher doses than those needed to reduce glucose levels (unpublished data). Moreover, AR231453, a prototype GPR119 agonist inhibited gastric emptying in GLP-1 receptor−/−, DIRKO, GLP-2 receptor−/− mice and even in presence of Y2 receptor antagonist in mice. Also, AR231453
reduced gastric emptying in wild type but not in GPR119−/− mice [75]. All these findings suggest that AR231456 inhibited gastric emptying independent of GLP-1 receptor, GLP-2 receptor and Y2 receptor. In contrast, GSK1292263 did not demonstrate effect on gastric emptying and body weight in rodent studies [59]. However, several other GPR119 agonists such as YH18421 and AS-1269574 showed significant reduction in feed intake and body weight loss in rodent studies upon chronic treatment [63, 65]. Recently, combination of GSK1299263 and metformin caused a synergistic weight loss in diet-induced obese mice suggesting potential benefit for obese diabetic patients [76]. Taken together, the above findings suggest that GPR119 agonists have the potential to inhibit feed intake, gastric emptying and body weight gain in rodent studies.

2.3.6 GPR119 Agonists: Anti-NASH Therapy

Since, GPR119 agonists stimulate incretin release, reduce feed intake, inhibit gastric emptying with additional benefit of body weight loss, they are a promising therapeutic option for the management of NASH. Some of the GPR119 agonists for e.g. HD0471953, GSK1292263, GSK2041706, AR-7947, AS-126574 and AS1907417 improved plasma lipid profiles in rodent studies [62, 65, 77-81]. Another novel GPR119 agonist, DA-1241 significantly attenuated hyperglycemia, hypertriglyceridemia and fatty liver in HFD/STZ diabetic mice model and high cholesterol fed rats [68, 82]. Recently, Yang JW et al. [50] demonstrated that GPR119 receptors were expressed in mouse hepatocytes and liver tissues. For the first time, authors demonstrated that MBX2982, a GPR119 agonist stimulated AMPK phosphorylation and inhibited the SREBP-1c expression in hepatocytes. Further, the down regulation of SREBP-1c caused reduction in lipogenesis related genes (FAS, ACC and SCD-1), thereby reducing hepatic fat accumulation in diet induced obese
mice (Figure 2.3.6). Furthermore, hepatic anti-lipogenesis effects of MBX2982 were abolished in liver specific GPR119 KO mice fed on high fat diet. In addition, MBX2982 also reduced plasma ALT, glucose, cholesterol and liver weight in obese mice [50]. Moreover, MBX2982 inhibited mRNA expressions of MCP-1 and pro IL-1β in choline deficient, amino acid fixed and HFD induced steatohepatitis model [83] and inhibited activation of hepatic stellate cells (unpublished results, [84]) suggesting a role in hepatic inflammation and fibrosis. A novel GPR119 agonist, Compound 9i also demonstrated reduction in plasma hepatic injury markers (ALT and AST), plasma lipid levels, hepatic steatosis and body weight loss without affecting feed intake in diet induced obese mice model [85]. Taken together, all these findings suggest that GPR119 agonists might be useful for the treatment of dyslipidemia and non-alcoholic fatty liver disease.

Figure 2.3.6 Inhibitory effect of GPR119 agonist on hepatic steatosis.
Ref: Yang JW et al. 2016 [50]
2.3.7 GPR119 Agonists: Clinical Pharmacology

Several GPR119 agonists have entered into phase I and II trials. However, not a single molecule has been tested in phase III clinical trials. Arena Pharmaceuticals, APD597 (JNJ-38431055) is an orally bioavailable, selective GPR119 agonist that was co-developed by Arena Pharmaceuticals and Johnson & Johnson. APD597 demonstrated incretin release in normal and diabetic patients. However, repeated administration caused poor glycemic efficacy and incretin release in diabetic patients [86, 87]. GSK1292263, a GPR119 agonist from GlaxoSmithKline in its phase II trial did not show significant effect on GLP-1, GIP, Glucagon, glucose, insulin levels and also failed to improve glucose control in type 2 diabetic patients when dosed alone or with Metformin or Sitagliptin. However, it caused significant increase in circulating total PYY levels [88]. PSN821 from Prosidion Limited (Phase II) was discontinued due to unknown reasons [59]. Another GPR119 agonist, MBX2982 (CymaBay Therapeutics) successfully reduced postprandial glucose levels in type 2 diabetic patients and increased insulin and incretin levels in a 4 weeks long phase II clinical trial; however, it was also discontinued [89, 90]. Recently, LEZ763, a novel GPR119 agonist demonstrated significant increase in GLP-1, GIP, and PYY levels but was unable to lower postprandial glucose levels significantly in diabetic patients. The increase in glucagon levels caused by LEZ763 was assumed to be the cause of undesirable clinical consequence in phase II trial [91]. Currently, BMS-903452, a novel GPR119 agonist has completed its phase I trial; however no further development has been reported since April 2016 [92].

The reasons for lack of clinical efficacy for GPR119 agonists still remain unknown, however for some of them like AR-7946 (preclinical) or GSK1192263, it was reported that they showed loss of efficacy in clinical trials either due to
tachyphylaxis or agonist induced desensitization of GPR119 receptors [59]. However, this is not the case for all other GPR119 agonists. For e.g. MBX2982 (phase II) showed reduction in glucose levels in diabetic patients. Thus, it suggests that tachyphylaxis appears to be a compound related (GSK1292263) rather than GPR119 target specific concern. Therefore, the lack of glycemic efficacy may be due to species differences in pharmacodynamics, or pharmacokinetic and limitations in physicochemical properties of the currently available compounds [84]. On the other hand, few GPR119 agonists such as APD668, YH18421 and DA-1241 did not show loss of efficacy even after repeated administration (once daily regimen) in rodent studies [56, 63, 68]. Interestingly, repeat administration of GSK1292263 significantly improved lipid profile in diabetic and non-diabetic dyslipidemic subjects [93, 94]. Recently, DS-8005a (Phase II) demonstrated significant reductions in triglyceride, total cholesterol, LDL cholesterol and a trend towards increase in HDL cholesterol levels in Japanese type 2 diabetes patients [95]. Therefore, the current focus has shifted to reprofiling of GPR119 agonists as anti-dyslipidemic agents even if they failed as anti-diabetic drugs [59].

2.4 Hypothesis

G-protein coupled receptor (GPR119) agonist was touted as a novel therapeutic target for the treatment of type 2 diabetes almost a decade ago. It is predominantly expressed in pancreatic β-cells and intestinal L-cells. GPR119 increases plasma GLP-1 and GIP levels in healthy and diabetic patients [85, 86]. GPR119 agonists act via a dual mechanism 1) activation of GPR119 receptor in pancreatic β-cells results in direct stimulation of glucose-dependent insulin secretion 2) activation of GPR119 in entero-endocrine cells results in stimulation of incretin release (GLP-1 & GIP),
leading to improved acute glucose tolerance [40, 41]. However, recently GPR119 has gained attention because of the emerging role of its receptor in lipid metabolism. GPR119 agonists have demonstrated improvement in lipid levels in preclinical and clinical settings, suggesting that they act as anti-dyslipidemic agent [62, 68, 77-81, 93, 94]. However, GPR119 agonists attenuate lipid profile through mechanisms that remain unclear. Some GPR119 agonists have demonstrated attenuation of fatty liver in obese and HFD/STZ diabetic mouse [50, 68], inhibited mRNA expressions of MCP-1 and pro IL-1β in choline deficient, amino acid fixed and HFD induced steatohepatitis model [83] and inhibited activation of hepatic stellate cells (unpublished results, [84]), suggesting that they have anti-steatotic, anti-inflammatory and anti-fibrotic activity. Thus, based on the above information, investigating the hypothesis of evaluating the per se effect of GPR119 agonist on postprandial lipemia, liver enzyme markers, hepatic steatosis, inflammatory and fibrosis markers in NASH condition is justified. Given the multifactorial nature of the disease, combination therapies may be needed to achieve best results in NASH management. Combination of GPR119 agonist (direct release of incretins) and DPPIV inhibitors (inhibit the degradation of incretins) may ultimately lead to increased levels of incretins which can improve postprandial lipemia and NASH. Similarly, to achieve more synergistic anti-dyslipidemic effect, combination of GPR119 agonist with PPAR-α agonist along with its anti-oxidant activity may be beneficial in the treatment of NASH. Therefore, taking into account the research gaps identified as above, we hypothesized that GPR119 receptor may represent a promising therapeutic target for the treatment of (NASH).
2.5 Aim

2.5.1 To investigate acute effects of APD668, a GPR119 agonist on postprandial lipemia in murine models

2.5.2 To investigate the effects of APD668, a GPR119 agonist alone or in combination with Linagliptin, DPPIV inhibitor or Fenofibrate, PPAR-α agonist, in chronic animal models of NASH listed below

- High Trans-Fat (HTF) diet induced NASH
- Low dose streptozotocin plus high fat diet induced NASH
- Methionine and Choline Deficient (MCD) diet induced NASH

2.6 References


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