Intraportal GLP-1 infusion increases nonhepatic glucose utilization without changing pancreatic hormone levels

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RESEARCH DESIGN AND METHODS

Animals and surgical procedures. Studies were carried out on 42-h-fasted mongrel dogs of either sex with a mean weight of 22.4 ± 0.5 kg. This length of fast produces a metabolic state resembling that in the overnight-fasted human and results in liver glycogen levels that are at a stable minimum (7). All animals were maintained on a diet of meat (Kal Kan, Vernon, CA) and chow (Purina Lab Canine Diet No. 5006; Purina Mills, St. Louis, MO) composed of 34% protein, 14.5% fat, 46% carbohydrate, and 5.5% fiber based on dry weight. The animals were housed in a facility that met American Association for Accreditation of Laboratory Animal Care guidelines, and the protocol was approved by the Vanderbilt University Medical Center Animal Care Committee.

Approximately 16 days before experimentation, a laparotomy was performed under general anesthesia (0.02 mg/kg buprenorphine HCl presurgery and ~1% isoflurane inhalation anesthesia during surgery) so that silastic catheters (Dow Corning, Midland, MI) for sampling could be placed into the hepatic portal vein, hepatic vein, and a femoral artery as previously described (19). At the same time, catheters to be used for infusion were inserted into a jejunal vein, a splenic vein, and the hepatic artery as previously described (19). Ultrasound flow probes (Transonic Systems, Ithaca, NY) were placed around the portal vein and hepatic artery. The catheters were filled with saline containing heparin (200,000 U/l; Abbott Laboratories, North Chicago, IL), their free ends were knotted, and they, along with the free ends of the flow probe leads, were placed into subcutaneous pockets. Approximately 2 days before each study, the animals’ health was determined by assessment of the leukocyte count (<18,000/mm³), hematocrit (>35%), appetite (as evidenced by consumption of daily ration), and stools.

On the morning of the experiment, the catheters and Doppler leads were exteriorized from their subcutaneous pockets using local anesthesia (2% lidocaine; Abbott Laboratories). The contents of each catheter were aspirated, and they were flushed with saline. Intravenous access was established in two peripheral veins.

Experimental design. The protocol consisted of a 100-min equilibration period (~140 to ~40 min), a 40-min basal sampling period (~40 to 0 min), and a 240-min experimental period (0–240 min). At t = -140 min, a continuous infusion of indocyanine green dye (0.076 mg/min; Sigma Chemical, St. Louis, MO), used as a backup method for hepatic blood flow measurement, was started. At t = 0, a glucose infusion (4 mg·kg⁻¹·min⁻¹) was started into the portal circulation via the jejunal and splenic catheters to activate the portal glucose signal (13). Glucose infusion through a leg vein was used to achieve and maintain an arterial plasma glucose clamp at 160 mg/dl. During the experimental period (0–240 min), saline was given intraperitoneally (CON; n = 8) or GLP-1 (1 pmol·kg⁻¹·min⁻¹) was given into the hepatic portal vein (POR; n = 11) or hepatic artery (HAT; n = 8). Intraportal GLP-1 infusion at this rate created arterial and portal vein plasma GLP-1 levels similar to those observed during an oral glucose load (14). Basal plasma GLP-1 levels were measured by RIA, as previously described (24). Plasma GLP-1 levels were measured by ELISA (Linco Research), which recognizes only GLP-1 (7–36) amide and GLP-1 (7–37), the active forms of GLP-1. Plasma free fatty acid levels were determined spectrophotometrically, with an assay (Wako Chemicals, Richmond, VA) adapted to the Multiprobe Integrated Fusion Gripper (PerkinElmer, Shelton, CT).

Calculations. Total glucose infusion rate (GIR) was calculated by adding the intraportal and peripheral glucose infusion rates. For all calculations, plasma glucose levels were converted to blood glucose levels using factors described elsewhere (20). Net hepatic glucose balance (NHGB) was calculated using the formula [H × Ft – (A × Fa + P × Fp)], where A, P, and H are the arterial, portal vein, and hepatic vein blood glucose concentrations, respectively, and Fa, Fp, and Ft are arterial, hepatic portal vein, and total hepatic blood flow, respectively. When determining NHGB, positive values represent net hepatic glucose production, whereas negative values represent net hepatic glucose uptake. Nonhepatic glucose uptake (non-HGU) was calculated as GIR + NHGB over the sampling period plus a correction for changes in the mass of the glucose pool (12). Hepatic GLP-1 fractional extraction was calculated by dividing hepatic GLP-1 uptake [t·(A × Fa + P × Fp) – H × Ft], by hepatic GLP-1 load [t·(A × Fa + P × Fp)], where A, P, and H are the arterial, portal vein, and hepatic vein plasma GLP-1 concentrations, respectively, and Fa, Fp, and Ft are arterial, hepatic portal vein, and total hepatic plasma flow, respectively.

Statistical analysis. All data are presented as means ± SE. Repeated-measures two-way ANOVA was used for time course analysis, with post hoc data analysis determined by Student-Newman-Kuels method. Remaining analysis was done with one-way ANOVA. Statistical significance was accepted at P < 0.05.

RESULTS

Plasma glucose levels. In response to glucose infusion there was an increase in plasma glucose levels in the artery (158 ± 1, 156 ± 1, and 156 ± 1 mg/dl) and portal vein (177 ± 2, 174 ± 1, and 176 ± 2 mg/dl) in CON, POR, and HAT, respectively (Fig. 1A). There were no differences among groups.

Plasma GLP-1 levels. Basal plasma GLP-1 levels were similar, regardless of group, in the artery (2.5 ± 1.7, 2.8 ± 0.4, and 3.7 ± 0.8 pM) in CON, POR, and HAT, respectively; the hepatic portal vein (2.4 ± 1.7, 2.9 ± 0.4, and 3.5 ± 0.7 pM), and hepatic vein (2.3 ± 1.8, 3.2 ± 0.4, and 3.9 ± 0.8 pM) (Fig. 1B). GLP-1 levels in the artery, hepatic portal vein, and hepatic vein (3.5 ± 1.6, 3.7 ± 1.4, and 3.5 ± 1.3 pM) did not change in response to the saline infusion. On the other hand, they rose in the artery (27.1 ± 2.4 and 23.4 ± 2.5 pM), the hepatic portal vein (50.0 ± 4.2 and 22.8 ± 3.1 pM), and the hepatic vein (41.9 ± 3.0 and 41.6 ± 5.8 pM) (POR and HAT, respectively) in response to infusion of GLP-1 into the hepatic portal vein or hepatic artery, respectively (Fig. 1B). It should be noted that, regardless of the site of GLP-1 infusion, the GLP-1 levels in peripheral (arterial) and liver sinusoidal (hepatic vein) blood were matched in the two GLP-1 infusion groups. Conversely, hepatic portal vein levels were markedly higher during portal vein GLP-1 infusion (Fig. 1B).

Hepatic GLP-1 fractional extraction. Due to extremely low levels of GLP-1 at baseline, hepatic fractional extraction of active GLP-1 was calculated only for the portal GLP-1 infusion group. The average hepatic GLP-1 fractional extraction for the POR group was ~0.08.
Glucose infusion rates. There was no significant difference in the glucose infusion rate required to maintain the clamp in the saline and hepatic artery GLP-1 infusion groups (6.0 ± 0.5 and 6.7 ± 1.0 mg·kg⁻¹·min⁻¹, average over final 2 h; Fig. 2). When GLP-1 was given intraportally, on the other hand, significantly more glucose was required (8.5 ± 0.7 mg·kg⁻¹·min⁻¹, average over the final 2 h) than with either saline or hepatic artery GLP-1 infusion (Fig. 2).

Plasma insulin and glucagon levels. The arterial plasma insulin levels in the basal period were similar (7 ± 1, 5 ± 1, and 9 ± 1 μU/ml in CON, POR, and HAT, respectively) in the three groups. Likewise, they rose similarly in response to the hyperglycemia brought about during the experimental period (to 24 ± 2, 23 ± 3, and 23 ± 3 μU/ml; Fig. 3A). Portal plasma insulin levels increased from baseline (26 ± 5, 16 ± 5, and 31 ± 9 to 82 ± 4, 75 ± 6, and 69 ± 8 μU/ml) in response to hyperglycemia (Fig. 4A). There was no statistical difference in the total area under the curve (AUC) in either arterial or portal plasma insulin among groups during the experimental (0–240 min) period (Figs. 3A, inset, and 4A, inset). The arterial plasma glucagon levels decreased significantly in CON, POR, and HAT during the experimental period (to 23 ± 2, 30 ± 3, and 25 ± 2 pg/ml, respectively) from their respective basal values (36 ± 3, 43 ± 4, and 36 ± 3 pg/ml) (Fig. 3B). Portal plasma glucagon levels also decreased from basal (50 ± 6, 51 ± 4, and 46 ± 3 pg/ml) during the experimental period (to 27 ± 1, 32 ± 3, and 28 ± 2 pg/ml) (Fig. 4B). There was no statistical difference in the total AUC for either the arterial or portal plasma glucagon during the experimental period (Figs. 3B, inset, and 4B, inset).

Hepatic blood flow, NHGB, and non-HGU. Hepatic artery blood flows during the basal period (7.2 ± 1.0, 5.4 ± 0.4, and 4.9 ± 0.7 ml·kg⁻¹·min⁻¹ in CON, POR, and HAT, respectively) and the experimental period (7.9 ± 0.7, 6.8 ± 0.4, and 6.4 ± 1.0 ml·kg⁻¹·min⁻¹) were not different among the groups. There was also no difference in hepatic portal vein blood flow in either the basal (22.7 ± 2.0, 28.9 ± 2.1, and 24.3 ± 1.8 ml·kg⁻¹·min⁻¹) or experimental periods (22.7 ± 1.8, 27.9 ± 1.9, and 25.1 ± 1.7 ml·kg⁻¹·min⁻¹). In the basal state, net hepatic glucose output was similar in all groups (1.6 ± 0.3, 2.0 ± 0.2, and 1.6 ± 0.1 ml·kg⁻¹·min⁻¹). In response to the hyperglycemic clamp the liver switched to net glucose uptake, with statistically greater net hepatic glucose uptake when GLP-1 was given into the hepatic artery (NHGB = −2.4 ± 0.4, −3.0 ± 0.4, and −3.9 ± 0.4 ml·kg⁻¹·min⁻¹ in CON, POR, and HAT, respectively, during final 2 h; Fig. 5A). Non-HGU was not different during saline or hepatic artery GLP-1 infusion (3.8 ± 0.7 and 3.0 ± 0.8 ml·kg⁻¹·min⁻¹, respectively, final 2 h), but it was significantly greater (5.5 ± 0.8 ml·kg⁻¹·min⁻¹, final 2 h) when GLP-1 was given into the hepatic portal vein (Fig. 5B).

Arterial plasma free fatty acids. Arterial plasma free fatty acid levels decreased similarly in response to glucose infusion (from 994 ± 127, 883 ± 80, and 1,073 ± 84 to 362 ± 111,
DISCUSSION

After a meal, intraportal GLP-1 levels are approximately twice those in peripheral blood (5). Therefore, GLP-1R in the hepatic portal vein are exposed to higher GLP-1 concentrations than receptors in other sites of the body. This makes the hepatic portal vein a potential site for initiation of some of GLP-1’s effects. Studies in rats (14) showed that an intraportal injection of GLP-1 resulted in increased afferent impulse from the hepatic branch of the vagus nerves. This suggests that GLP-1 can initiate a neural signal within the hepatic portal vein that could result in actions at other site in the body. In the present study our goal was to determine which, if any, of GLP-1’s effects are initiated at this site. The experimental design was such that the action of GLP-1 on gastric emptying and β-cell proliferation was of no consequence. In addition, by including groups in which GLP-1 was infused into either the hepatic artery or the hepatic portal vein, we were able to differentiate between effects resulting from elevations of GLP-1 within the liver vs. those within the portal vein. Therefore, we were able to assess the effects of portal vein GLP-1 per se on pancreatic hormone secretion and on the rate of glucose uptake by the liver and nonhepatic tissues.

Fig. 3. A: arterial plasma insulin levels during the basal period (−40 to 0 min) and during the infusion of saline or GLP-1 into the hepatic portal vein or hepatic artery (0 to 240 min). There was a significant increase in insulin levels in each group during the experimental period when compared with respective basal period values (P < 0.05); inset: AUC for experimental period. There were no differences among groups upon analysis of the time course or experimental period area AUC. Data are expressed as means ± SE. B: arterial plasma glucagon levels during the basal period (−40 to 0 min) and during the infusion of saline intraportally or GLP-1 into the hepatic portal vein or hepatic artery (0 to 240 min); inset: AUC during the experimental period. There was a significant decrease in glucagon levels in each group during the experimental period when compared with respective basal period values (P < 0.05), but there were no differences among groups upon analysis of the time course or experimental period AUC. Data are expressed as means ± SE.

Fig. 4. A: portal plasma insulin levels during the basal period (−40 to 0 min) and during the infusion of saline or GLP-1 into the hepatic portal vein or hepatic artery (0 to 240 min). There was a significant increase in insulin levels in each group during the experimental period when compared with respective basal period values (P < 0.05); inset: AUC for experimental period. There were no differences among groups upon analysis of the time course or experimental period AUC. Data are expressed as means ± SE. B: portal plasma glucagon levels during the basal period (−40 to 0 min) and during the infusion of saline intraportally or GLP-1 into the hepatic portal vein or hepatic artery (0 to 240 min); inset: AUC during the experimental period. There was a significant decrease in glucagon levels in each group during the experimental period when compared with respective basal period values (P < 0.05), but there were no differences among groups upon analysis of the time course or experimental period AUC. Data are expressed as means ± SE.
intrapanoral GLP-1 increases nonhepatic glucose uptake

**A**

**Fig. 5.** A: net hepatic glucose balance (NHGB) during the basal period (−40 to 0 min) and during the infusion of saline or GLP-1 into the hepatic portal vein or hepatic artery (0−240 min). Rates in each group were significantly decreased (P < 0.05) during the infusion of saline or GLP-1 into the hepatic portal vein or hepatic artery (0−240 min) compared with their respective basal period values. Data are expressed as means ± SE. *P < 0.05 vs. CON; #P < 0.05 vs. POR. B: nonhepatic glucose uptake (non-HGU) during the infusion of saline or GLP-1 into the hepatic portal vein or hepatic artery (30−240 min). Data are the average of values over 30-min segments and are expressed as means ± SE. *P < 0.05 vs. CON; +P < 0.05 vs. HAT.

A significantly greater glucose infusion rate (8.5 ± 0.7 vs. 6.7 ± 1.0 mg·kg⁻¹·min⁻¹, average over the final 2 h) was required to maintain the glucose clamp when GLP-1 was given intrapanorally than when it was given at the same rate into the hepatic artery (Fig. 2) despite there being no difference in pancreatic hormone levels (Figs. 3 and 4). This occurred even though the arterial and hepatic vein GLP-1 levels were identical in the two groups (Fig. 1B); therefore, the difference in the glucose infusion rate must be attributed to the difference in the hepatic portal vein GLP-1 levels (48.7 ± 4.7 vs. 22.8 ± 3.1 pM). The hepatic portal vein GLP-1 concentrations increased 10-fold when GLP-1 was given into the hepatic artery vs. 20-fold when it was given into the portal vein (Fig. 1B). The increase (over saline) in the peripheral glucose infusion rate required in the portal GLP-1 infusion group was three times greater than the increase in the glucose infusion rate that was required in the hepatic artery infusion group. This difference in glucose infusion rate was slow to develop, reaching a maximum at −120 min after the start of GLP-1 infusion. Thereafter, the difference between groups was maintained (Fig. 2).

The delay in the onset of the effect of portal-delivered GLP-1 occurred despite the fact that GLP-1 levels were elevated in a square wave fashion. An increase (over saline) in the glucose infusion rate actually occurred as early as 40 min after the start of portal GLP-1 infusion, but it did not reach significance until 120 min (Fig. 2). The delay in the rise in the glucose infusion rate indicates that the pharmacokinetic time course of GLP-1 differs from the time course of the pharmacodynamic response to its infusion. This was also evident in an earlier study (14) in which a bolus of GLP-1 given into hepatic portal vein of the rat caused an ever-increasing rise in afferent neural discharges over time. These findings suggest that certain effects of GLP-1 may last for a longer period of time than the increment during which GLP-1 blood level is increased. It has been shown that postprandial GLP-1 levels remain elevated for as long as 3 h in the human (22) and 6 h in the dog (Johnson KM, Edgerton DS, Rodewald T, Scott M, Farmer B, Neal D, Cherrington AD, and Moore MC, unpublished data). The present data suggest that the impact of the rise in GLP-1 might go on for an even longer period of time. The mechanistic explanation for this slow onset of action may relate to persistent changes in neural firing or the time required for the synthesis of regulatory proteins.

Given that intrapanoral infusion of GLP-1 increased whole body glucose disposal in the absence of a change in plasma insulin, the question thus arises as to which tissues were responsible for the increase. By placing catheters across the liver, one can separate whole body glucose uptake into its hepatic and non-hepatic components. There was only a small increase (3.0 ± 0.4 vs. 2.4 ± 0.4 mg·kg⁻¹·min⁻¹, not significant) in net hepatic glucose uptake in the animals that received intrapanoral GLP-1 vs. saline (Fig. 5A). As a result, it can be concluded that the increase in whole body glucose uptake seen in those animals was due primarily to an increase in non-hepatic glucose uptake. This is confirmed by our observation that the calculated rate of non-hepatic glucose uptake was significantly increased in the presence of intrapanoral as opposed to hepatic artery GLP-1 infusion (3.0 ± 0.8 vs. 5.5 ± 0.8 mg·kg⁻¹·min⁻¹, respectively, during the final 2 h of the study; Fig. 5B). It is also in agreement with previously reported studies (2, 3), which indicated that portal vein GLP-1 receptors regulate non-hepatic glucose uptake in the mouse in the presence of an intrapanoral glucose infusion. A previous study (5) conducted in our laboratory showed that a physiological increase in GLP-1 resulting from intrapanoral infusion of the peptide at the same rate as that used here, when brought about with the pancreatic hormones clamped at levels similar to those observed in the current study, caused a small increase in net hepatic glucose uptake (~0.8 mg·kg⁻¹·min⁻¹), much like in the present study, but, contrary to the present results, GLP-1 infusion in the clamp studies had no effect on nonhepatic glucose uptake. However, the duration of the intrapanoral GLP-1 infusion in the previous study was only 90 min (5), perhaps explaining the fact that we did not see a significant increase in nonhepatic glucose uptake (i.e., in the present study the effect did not become significant until 120 min). In addition, in our
previous study, glucose was clamped using only a peripheral infusion (i.e., no portal glucose delivery). It has been clearly shown that when glucose is delivered intraportally it decreases afferent vagal firing (18) and causes an increase in net hepatic glucose uptake and a decrease in nonhepatic glucose uptake (4). Portal delivery of GLP-1 increases vagal afferent firing (14); thus it is possible that, in the presence of portal glucose delivery, GLP-1 can bring about effects that would not be observed in the absence of portal glucose delivery.

Taking the results from our previous study (5) and the current study together it would appear that a physiological increase in GLP-1 secretion can bring about two effects, each independent of the actions of GLP-1 on the endocrine pancreas. First, GLP-1 can have a direct, but modest, effect on the liver per se to increase net hepatic glucose uptake. This is seen independently of whether the rise in liver sinusoidal GLP-1 results from input via the hepatic artery or the hepatic portal vein (5). It can best be seen by examining the hepatic artery GLP-1 infusion data (i.e., those without the added action of portal vein GLP-1 signaling). In our earlier study (5), net hepatic glucose uptake increased by ~1.0 mg·kg⁻¹·min⁻¹ in response to hepatic artery GLP-1 infusion, whereas in the present study it increased by 1.5 mg·kg⁻¹·min⁻¹ (2.4 ± 0.4 vs. 3.9 ± 0.4 mg·kg⁻¹·min⁻¹). This was despite the fact that there were no differences in plasma insulin or glucagon level in the presence of GLP-1, compared with the control, in either study. The second effect of GLP-1 relates to its delivery into the portal vein. There it tends to decrease net hepatic glucose uptake (from 3.9 ± 0.4 to 3.0 ± 0.4 mg·kg⁻¹·min⁻¹) and to increase nonhepatic glucose uptake (from 3.0 ± 0.8 to 5.5 ± 0.8 mg·kg⁻¹·min⁻¹). The question then arises as to why a 20-fold rise in portal vein GLP-1 would bring about this effect and a 10-fold increase would not. This could have resulted from a threshold effect such that a 10-fold increase simply did not bring about a big enough change for us to detect. Alternatively, the portal vein concentration difference in GLP-1 may be detected and bring about a unique response.

It has been well established (16) that exogenously infused GLP-1 acts as an incretin in both healthy humans and those with type 2 diabetes. As noted above, however, in the current studies there was no difference in arterial or portal plasma insulin levels in the presence or absence of GLP-1 infusion regardless of whether the peptide was given intraportally or via the hepatic artery (Fig. 3A). This is in agreement with earlier data (9) indicating that dogs that received a systemic infusion of glucose to simulate postprandial peripheral glucose levels showed no change in insulin levels when a peripheral GLP-1 infusion was added to create a physiological increase in GLP-1 levels.

Postprandial increases in peripheral plasma GLP-1 levels in the human and dog are very similar (both reaching levels of ~10–15 pmol/L); however, we did not observe greater insulin levels in the presence vs. the absence of GLP-1 in the current study despite the fact that our GLP-1 levels were designed to match postprandial levels. There are several possible explanations for our failure to observe an incretin effect of GLP-1. There is some evidence that the GLP-1 clearance in the human and the dog may be different. It has been shown that an infusion rate of ~0.3 pmol·kg⁻¹·min⁻¹ is required to create a postprandial rise in total peripheral GLP-1 levels in the human (15), whereas the dog requires 3–4 times that rate to simulate postmeal levels of active GLP-1 (5). This suggests greater clearance of GLP-1 in the dog such that, for a given infusion rate, the plasma levels would be lower in the dog; therefore, the 1 pmol·kg⁻¹·min⁻¹ infusion rate used here might result in significantly higher GLP-1 levels in humans, which could induce significantly greater effects at the β-cell.

On the other hand, there may be a species difference in β-cell sensitivity to GLP-1, because it has been shown that in humans an infusion of 0.15 pmol·kg⁻¹·min⁻¹, in the presence of ~180 mg/dl plasma glucose levels, can augment glucose-stimulated insulin secretion (15), whereas in the current study an infusion rate of 1 pmol·kg⁻¹·min⁻¹ in the presence of ~160 mg/dl plasma glucose did not change plasma insulin levels. This raises the question of whether endogenously released GLP-1 acts as an incretin hormone in the dog. It could still do so if endogenously released GLP-1 initiates an incretin signal upstream from our infusion site in closer proximity to the L cells from which it is released. It is known (8) that a large portion of GLP-1 is degraded in the gut by DPP IV in the brush-border membrane prior to its reaching the hepatic portal vein; therefore, we may not have observed an increase in insulin in the presence of GLP-1 due to the fact that active GLP-1 levels at the gut were not high enough to induce an incretin effect.

The data presented here also indicate that GLP-1 produced no additional suppression of the plasma glucagon level in response to hyperglycemia (Figs. 3B and 4B). Our data thus support the concept that GLP-1 infusion decreases plasma glucagon only in the presence of inappropriately elevated levels of the hormone, as previously observed in patients with diabetes (11, 16).

As previously mentioned, an advantage to our model is the ability to determine substrate balance across the liver. We were able to determine that ~8% of active GLP-1 is degraded as it traverses the liver in the healthy dog. This degradation represents a combination of GLP-1 that is degraded by the liver per se and the amount that is exposed to and degraded by DPP-IV in plasma during hepatic transit. The measured levels of GLP-1 in the hepatic portal vein were slightly below the value predicted given portal vein plasma flow and the GLP-1 infusion rate. This is undoubtedly the result of imperfect mixing of the infused in the portal blood. Were recovery of GLP-1 to have been perfect, the portal vein GLP-1 levels would have been modestly higher and the amount of GLP-1 lost in transit through the liver could have been 18%. Thus it would appear that <20% of active GLP-1 is removed from the blood as it traverses the liver.

In conclusion, the current study shows that delivery of a physiological amount of GLP-1 into the hepatic portal vein (but not the hepatic artery) increased whole body glucose uptake in the absence of an effect on plasma insulin or glucagon levels. This increase was due primarily to an augmentation of nonhepatic glucose uptake.

At this point, the mechanism by which this effect comes about is unclear. Nevertheless, the current results further support the concept that the nonincretin effects of GLP-1 are also important in its regulation of glucose metabolism in vivo.
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