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Diabetes Mellitus And Reparative Response Of Dental Pulp

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SUMMARY

Anatomically, dental pulp is connective tissue and specific microcirculatory system with significant reparatory abilities intending to preserve pulp vitality. Various therapeutic approaches in the treatment of affected pulp may be compromised by various factors leading to treatment failure. Due to microcirculatory system disorders, treatment of affected dental pulp in patients with diabetes mellitus (DM) is additional challenge. The function and levels of growth factors could be altered in various diabetic tissues including dental pulp. Among them are growth factors important for reparative response of the pulp. There are experimental evidences that DM impede dental pulp reparation. Therefore, clinical procedures aiming to preserve vitality of diabetic dental pulp should be applied with caution.

The aim of this paper is to present basic factors and parameters that affect reparative response of dental pulp in patients with DM.

Keywords: dental pulp; diabetes mellitus; growth factors

INTRODUCTION

Dental pulp is a connective tissue that has some unique characteristics. Namely, it has specific microcirculatory system with no lateral blood vessel branches. Also, dental pulp is located within solid dentinal walls that cannot accept any significant change of its volume. These features make it very prone to irreversible inflammatory changes shortly after the impact of noxious stimuli. This can be significantly intensified in persons with diabetes mellitus (DM) known for their tissue vulnerability caused by macro- and micro-circulatory disorders.

Dental pulp has significant reparatory abilities that are important for therapeutic approaches aiming to preserve pulp vitality. These treatment modalities may be compromised by various factors leading to treatment failure. Therefore, these factors should be well known and described in order to establish appropriate indication for maintaining pulp vitality. Diabetic dental pulp, with possible various pathological changes, may present additional challenge for these treatment modalities.

The aim of this paper is to present basic factors and parameters with influence on reparative response of dental pulp in patients with diabetes mellitus.

REPARATIVE RESPONSE OF DENTAL PULP

The primary role of pulp is to produce dentin, but it is well known that this tissue has several functions: nutritive, sensory, defensive and reparative. Ability to repair is of special clinical interest because it has fundamental influence on all therapeutic procedures aiming to maintain pulp vitality. Reparative response of dental pulp is modified by morphological and functional pulp status (younger or older subjects, specific location, previous history of reparation process, etc). Reparative response depends on the type and intensity of harmful stimuli [1]. Specificity of pulp tissue compared to other connective tissues is dentin production up regulated during the repair process known as tertiary dentinogenesis. The layers of dentin are deposited on the pulp-dentinal interface, particularly towards noxious stimuli. The aim of this process is to protect pulp tissue by blocking harmful effects. The prerequisite for this process is localized, controlled and mild inflammation that will allow spreading blood vessels and providing adequate nutrient supply for up-regulated pulp secretory activity [2].

Tertiary dentinogenesis may progresses in two completely different ways depending on the intensity of noxious stimuli. In mild to moderate stimuli (for example shallow caries lesion) odontoblasts, specific secretory cells of dental pulp, may survive and increase their activity forming layers of tertiary dentin [3]. This process is called reactionary dentinogenesis. In case of strong stimuli, odontoblasts will not survive. Progenitor pulp cells will then activate, migrate and differentiate into odontoblast-like cells. These cells will form layers of new dentin in complex process known as reparative dentinogenesis [4]. Various signaling molecules regulate both reactionary and reparative dentinogenesis.

Although the process of tertiary dentinogenesis is well recognized and described, cellular and molecular mechanisms of its regulation are still not fully identified. It is known that specific cells conduct tertiary dentinogenesis. The cell lines involved in up-regulated dentin production

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are odontoblasts or odontoblast- like cells. The origin of the later ones is still unclear, but they are most probably derived from progenitor pulp cells (stem cells, Rougett pericytes, etc) [5]. Tziafas et al. have found that dentinogenetic activity of odontoblast- like cells may occur only in pulpal environment indicating that there are specific stimulators in pulp intercellular substance that initiate and conduct this process[6]. It is now well known that these "stimulators" are growth factors (GF).

THE ROLE OF GROWTH FACTORS IN PULP REPARATION

GF are signaling molecules that have the structure of polypeptides or small proteins. Cells produce GF and their regulatory function is achieved through binding to specific trans-membrane receptors. GF may activate receptors on cells they have been excreted by (autocrine mode of regulation), or they may react with receptors of adjacent cells (paracrine mode of regulation). When GF binds to extracellular domain of receptor, the intracellular enzymatic part will activate cascade of specific cellular reactions. In most cases this will lead to expression of specific genes and consequent synthesis of proteins included in regulation of particular cellular event [7]. Non-transcriptional responses may also occur as a result of GF activity, leading to activation of already existing proteins.

Numerous experimental evidences indicate that the key GF's with regulatory role in processes of pulp reparation are members of transforming growth factor β (TGF-β) superfamily[8]. Bone morphogenetic proteins (BMP), members of TGF-β superfamily, are also identified within pulp tissue[9]. Angiogenic GF's are of special importance, having in mind the need for adequate vascular supply in the pulp with up-regulated secretory activity. Vascular endothelial growth factor (VEGF) is the most prominent angiogenic GF, identified in dental pulp tissue[10]. Besides pulp tissue, all of this GF was identified in dentin matrix, too [11, 12]. During the progression of caries lesion, or as a result of pulp capping therapy, they will be released from dentin matrix and take role in regulation of dentinogenetic events [13].

DIABETES MELLITUS

DM is systemic metabolic disorder with hyperglycemia as main characteristic. It may be the result of pancreatic β cells dysfunction (DM type 1), or increased tolerance of cells and tissues to secreted insulin (DM type 2). DM, specifically type 2, is one of the most prevalent systemic diseases in human population [14]. DM is specific for its numerous complications that may seriously damage patients' life quality. All DM complications are in fact pathologic result of either macrovascular or microvascular changes in different tissues and organs. Therefore, these complications may be classified as macrovascular (atherosclerosis of cardiac blood vessels, coronal disease, etc.) or microvascular (diabetic retinopathy, diabetic nephropathy, etc.) [15].

There are significant physiological changes in DM. The main pathophysiological mechanism of changes during DM is mitochondrial overproduction of superoxides due to hyperglycemia which results in increase of tissue oxidative stress [15]. This leads to activation of specific pathophysiological mechanisms, signed to be direct promoter of histological changes. Activation of protein kinase C and formation of glycozilated end products are the main mechanisms to provoke changes in levels and function of different GF, contributing profoundly to the specific diabetic pathology [15].

Vascular endothelial growth factor (VEGF) is the most prominent GF responsible for diabetic complications. In physiological conditions it is responsible for vasculogenesis, angiogenesis and processes associated with them [16]. The levels and function of VEGF is altered in tissues and organs during DM. There are tissues with up-regulation of this GF leading to complications with extensive pathological hyper-angiogenesis such as diabetic retinopathy. On the other hand there are tissues where VEGF is down-regulated causing complications based on insufficient blood supply such as wound healing difficulties [17].

DM also provokes changes in TGF-β superfamily members [15]. Bone morphogenetic protein 2 (BMP-2), one of the members of this GF group, has significant influence on a specific pathological change in DM. Namely, BMP-2 is up-regulated in walls of diabetic blood vessels causing differentiation of osteoblasts and ectopic vascular calcifications. This is the main mechanism for atherosclerosis and similar changes in vascular beds to occur in DM [18, 19].

THE EFFECTS OF DM ON DENTAL PULP

DM may cause various pathological changes in oral tissues. Most of the studies on oral status in diabetic patients reported changes in oral mucosa and marginal periodontal tissues [14]. Endodontic research about the effect of DM on dental pulp is very scarce. Epidemiological studies reported higher prevalence of pulp and periapical diseases in diabetic patients[20], while Wang et al. [21] found higher frequency of tooth extraction after endodontic therapy in patients with DM, suggesting lower success rate of root canal treatment. Amatyakul et al. [22] found lowered blood flow in diabetic pulp, while Inagaki et al. reported higher prevalence of intrapulpal calcifications [23]. Histological studies showed increased thickness of blood vessel basement membrane, reduction in collagen level of intercellular substance and signs of chronic inflammation and angiopathy [24].It was concluded in the study of Garber et al. that pulp in diabetic rats had compromised reparatory response resulting in chronic pulp inflammation and reduced dentin bridge formation in comparison to pulp in non-diabetic rats [25]. Histological studies revealed higher concentrations of inflammatory mediators and enzymes in diabetic pulp, as well as oxidative stress parameters indicating higher level of reactive oxygen species in diabetic pulp comparing to non-diabetic one [26, 27]. Ilić et al. analyzed human diabetic dental pulp and

found significant changes in levels of VEGF and BMP-2,GF's important for pulp reparative response [28].

VEGF is of great importance for microcirculatory system of dental pulp. The expression of VEGF and its receptors has been identified in pulp using polymerase chain reaction (PCR) method[29, 30] as well as immunohistochemical identification [31]. Increased expression of VEGF has been noticed during some pathological conditions of dental pulp such as inflammation, injury and hypoxia [32-34].

BMP-2 is GF with significant role in dental pulp functions. Expression of BMP-2 in dental pulp was demonstrated immunohistochemicaly [35] and by PCR method [9, 36]. This GF is responsible for odontoblast differentiation of pulp stem cells and for up-regulation of odontoblast secretion in primary, secondary and tertiary dentinogenesis [37, 38].

Changes in these GF levels could be of special interest when analyzing the effect of DM on pulp reparative response. Their altered levels in DM could provoke inadequate reaction of dental pulp on noxious stimuli. This is in concordance with the investigation of Garber et al. [25] that provided evidences that DM impede dental pulp reparation on rat model and with empirically known fact from practice that reactions of diabetic dental pulp on capping procedures may be very unpredictable.

CONCLUSION

Clinical dilemma whether to conduct pulp capping or to extend indications for pulpectomy in medically compromised patients with DM still exists. Fundamental physiological and clinical data on this problem are scarce. Extensive investigation should be conducted to reveal and describe cellular and molecular mechanisms of recognized changes in pulp reparative response during DM. Although these mechanisms are still insufficiently known, therapeutic procedures in order to preserve the pulp vitality in DM patients should be realized with caution.

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Dijabetes melitus i reparativni odgovor zubne pulpe

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KRATAK SADRŽAJ
Zubna pulpa je vezivno tkivo i poseban mikrocirkulatorni sistem sa značajnim reparatornim sposobnostima u cilju očuvanja njenog vitaliteta. Terapijski postupci u lečenju obolele pulpe mogu da budu kompromitovani delovanjem brojnih faktora koji mogu uticati na ishod lečenja. Zubna pulpa kod pacijenata sa dijabetes melitusom (DM), zbog mikrocirkulatornih poremećaja često predstavlja poseban terapijski izazov. Poznato je da funkcije i nivoi faktora rasta mogu biti promenjeni u dijabetičnim tkivima, pa samim tim i u zubnoj pulpi. Ovde su od najveće važnosti faktori rasta značajni za regulaciju reparatornog odgovora pulpe. Postoje eksperimentalni dokazi da DM umanjuje reparativnu aktivnost zubne pulpe, pa zbog toga kliničke procedure vezane za očuvanje vitaliteta dijabetične zubne pulpe treba realizovati uz značajne mere opreza.
Cilj ovog rada je da se predstave osnovni faktori i parametri koji utiču na reparatorni odgovor pulpe zuba kod obolelih od DM.
Ključne reči: zubna pulpa; dijabetes mellitus; faktori rasta

UVOD

Zubna pulpa je vezivno tkivo koje poseduje posebne karakteristike jer predstavlja jedinstven mikrocirkulatorni sistem bez kolateralnih grana. Takođe, pulpa je smeštena unutar čvrstih dentinskih zidova, što onemogućava bilo kakvu promenu njenog volumena. Ove osobine uslovljavaju ireverzibilne inflamatorne promene u kratkom vremenskom periodu nakon delovanja štetnih nadražaja. Ova sklonost je posebno potencirana kod osoba obolelih od dijabetesa melitusa (DM) usled pojačane sklonosti ka tkivnim oštećenjima uzrokovanu prisutnim promenama na velikim i malim krvnim sudovima.

Zubna pulpa ima značajne reparatorne sposobnosti, što je značajno za terapijske pristupe koji imaju za cilj očuvanje njenog vitaliteta. Međutim, terapijski modaliteti mogu biti kompromitovani brojnim uticajima koji vode neuspehu tretmana. Zbog toga je veoma važno poznavati ove faktore radi postavljanja pravilne indikacije, ali i realizacije terapijskih postupaka u cilju očuvanja vitaliteta ovog tkiva. Zato dijabetična zubna pulpa, sa brojnim patološkim promenama, predstavlja poseban izazov u terapiji.

Cilj ovog rada je da se predstave osnovni faktori i parametri koji utiču na reparatorni odgovor pulpe zuba kod obolelih od DM.

REPARATORNI ODGOVOR ZUBNE PULPE

Primarna uloga zubne pulpe je da stvara dentin. Reparatorna sposobnost pulpe je predmet posebnog kliničkog interesovanja jer leži u osnovi svih terapijskih procedura koje imaju za cilj očuvanje vitaliteta. Ovaj odgovor zubne pulpe može biti modifikovan njenim morfološkim i funkcionalnim stanjem (pulpa zuba starijih ili mlađih osoba, lokalizacija pulpe, prethodni reparatorni procesi itd.), a značajno zavisi od vrste i intenziteta štetnog nadražaja [1]. Specifičnost pulpe u odnosu na druga vezivna tkiva je produkcija dentina, koja je povećana tokom reparacije (tercijarna dentinogeneza). Slojevi novog dentina nastaju na pulpo-dentinskom spoju, prvenstveno u smeru delovanja štetnog nadražaja sa ciljem zaštite pulpnog tkiva mogućim blokiranjem štetnih uticaja. Preduslov za odvijanje ovog procesa je lokalizovana, kontrolisana i blaga zapaljenska reakcija koja dovodi do širenja mreže malih krvnih sudova, što sledstveno obezbeđuje adekvatno snabdevanje nutrijentima neophodnim za povećanu sekretornu aktivnost pulpe [2].

Tercijarna dentinogeneza može da se odvija u dva potpuno različita pravca i zavisi od intenziteta štetnih nadražaja. Kod blagih i umerenih nadražaja (na primer plitka karijesna lezija) odontoblasti mogu da prežive i pojačaju svoju sekretornu aktivnost formirajući nove slojeve tercijarnog dentina [3] (reaktivna dentinogeneza). U slučaju jakih stimulusa, odontoblasti bivaju oštećeni, pa se tada progenitorne ćelije pulpe aktiviraju, migriraju i diferenciraju u ćelije slične odontoblastima. Ove ćelije potom formiraju slojeve novog dentina u procesu reparativne dentinogeneze [4]. Procesi kako reaktivne tako i reparatorne dentinogeneze su regulisani brojnim signalnim molekulama.

Iako je tercijarna dentinogeneza process koji je jasno prepoznat i dobro opisan, ćelijski i molekularni mehanizmi njegove regulacije nisu još uvek potpuno jasni. Poznato je da ove procese sprovode specifične ćelije. Ćelijske vrste neposredno odgovorne za povećanu pulpnu sekreciju su odontoblasti i ćelije slične odontoblastima. Poreklo ovih drugih još uvek je nedovoljno jasno, ali je najverovatnije da nastaju iz progenitornih pulpnih ćelija (stem ćelija, Rudžetovih (*Rougett*) pericita i sl.) [5]. Cafas (*Tziafas*) i sar. su utvrdili da odontoblastima slične ćelije mogu da stvaraju dentin samo u okuženju pulpnog tkiva, što ukazuje da u međućelijskoj supstanci pulpe postoje specifični stimulatori koji iniciraju i vode ovaj proces [6]. Danas se zna da su ovi tkivni stimulatori u stvari faktori rasta (FR).

ULOGA FAKTORA RASTA U REPARACIJI ZUBNE PULPE

Faktori rasta su signalne molekule koje su po svojoj hemijskoj strukturi polipeptidi ili mali proteini. Oslobađaju ih ćelije, a njihova regulatorna uloga se ostvaruje vezivanjem i aktivacijom specifičnih transmembranskih receptora. FR se mogu vezati za receptore na istoj ćeliji koja ih je proizvela (autokrina vrsta dejstva) ili za receptore na susednim ćelijama (parakrina vrsta dejstva). Kada se FR veže za vanćelijski deo receptornog molekula (tzv. ekstraćelijski domen), unutarćelijski enzimski deo receptora će započeti kaskadu specifičnih ćelijskih reakcija. U najvećem broju slučajeva ova kaskada reakcija dovodi do ekspresije specifičnog gena i sledstvene sinteze proteina odgovornih za regulaciju određenog ćelijskog procesa [7]. Kao rezultat aktivnosti FR mogu se desiti i netranskripcioni odgovori koji dovode do aktivacije već postojećih proteina u ćeliji.

Veliki broj eksperimentalnih studija ukazuje da su ključni FR za regulaciju procesa reparacije pulpe oni iz familije faktora rasta transformacije β (TGF-β) [8]. Kostni morfogenetski proteini,

koji su inače članovi TGF-β familije, takođe su identifikovani u tkivu pulpe [9]. Angiogeni FR imaju poseban značaj, imajući u vidu potrebu za adekvatnim vaskularnim snabdevanjem pulpe koja ima povećanu sekretornu aktivnost. Faktor rasta vaskularnog endotela (VEGF) najznačajniji je angiogeni FR identifikovan u pulpi [10]. Osim tkiva zubne pulpe, svi pomenuti FR identifikovani su i u dentinskom matriksu [11, 12]. Tokom razvoja karijesne lezije, ali i kao posledica terapijskih postupaka prekrivanja pulpe, ovi faktori se oslobađaju iz dentinskog matriksa i ulaze u sledstvene procese regulacije [13].

DIJABETES MELITUS

Dijabetes melitus (DM) je sistemsko metaboličko oboljenje sa hiperglikemijom kao glavnom karakteristikom. Ono može nastati kao rezultat disfunkcije β ćelija pankreasa (DM tipa 1), ili kao rezultat povećane tolerancije ćelija i tkiva na insulin (DM tipa 2). DM, prvenstveno tipa 2, jedno je od najzastupljenijih sistemskih oboljenja u ljudskoj populaciji [14]. DM je posebno značajno oboljenje zbog brojnih komplikacija koje mogu ozbiljno da ugroze kvalitet života pacijenata. Sve komplikacije DM su u suštini posledica makrovaskularnih ili mikrovaskularnih promena u različitim tkivima i organima i zato se mogu klasifikovati kao makrovaskularne (ateroskleroza velikih krvnih sudova, koronarna bolest i sl.) i mikovaskularne (dijabetična retinopatija, dijabetična nefropatija i sl.) [15].

Međutim, postoje i suštinske fiziološke promene kod obolelih od DM. Osnovni patofiziološki mehanizam promena tokom DM je hiperprodukcija superoksida u mitohondrijama, koja nastaje kao posledica hiperglikemije i dovodi do povećanja oksidativnog stresa u tkivima [15]. Ovo vodi u aktivaciju specifičnih patofizioloških mehanizama, koji se smatraju direktnim pokretačima histoloških promena. Aktivacija proteinske kinaze C i stvaranje glikozilisanih završnih produkata metabolizma glavni su mehanizmi koji izazivaju promene u funkcijama različitih FR i značajno doprinose specifičnoj dijabetičnoj patologiji [15].

VEGF je najznačajniji FR odgovoran za razvoj dijabetičnih komplikacija. U fiziološkim uslovima, on je odgovoran za vaskulogenezu, angiogenezu i njima povezane procese [16]. Nivoi i funkcije VEGF su izmenjeni u tkivima i organima tokom DM. Postoje tkiva sa povišenom aktivnošću ovog FR, što dovodi do komplikacija usled ekstenzivne patološke angiogeneze kao kod dijabetične retinopatije. Sa druge strane, ima tkiva u kojima je aktivnost VEGF snižena izazivajući komplikacije usled neadekvatnog snabdevanja krvlju, kakvo je otežano zarastanje rana [17].

DM izaziva promene i u aktivnosti TGF-β familije [15]. Kostni morfogenetski protein 2 (BMP-2) ima značajan uticaj na razvoj specifičnih patoloških promena tokom DM. Naime, BMP-2 ima pojačanu aktivnost u zidovima dijabetičnih krvnih sudova i utiče na diferencijaciju osteoblasta i ektopične kalcifikacije. Ovo je glavni mehanizam ateroskleroze i sličnih promena koje nastaju na krvnim sudovima tokom DM [18, 19].

EFEKTI DM NA ZUBNU PULPU

DM dovodi do brojnih patoloških promena na oralnim tkivima. Većina studija vezanih za oralno stanje dijabetičara ukazala je na promene na oralnoj mukozi i marginalnom parodoncijumu [14]. Endodontske studije o efektima DM na zubnoj pulpi veoma su retke. Epidemiološke studije su pokazale veću prevalenciju pulpnih oboljenja i oboljenja apeksnog parodoncijuma [20], dok suVang (*Wang*) i sar. [21] uočili veću učestalost ekstrakcija zuba nakon sprovedenog endodontskog tretmana kod pacijenata sa DM. Amatjakul (*Amatyakul*) i sar. [22] našli su smanjen protok krvi u dijabetičnoj pulpi, dok su Inagaki i sar. utvrdili veću učestalost intrapulpnih kalcifikacija [23]. Studije na tkivnom nivou pokazale su zadebljalost bazalne membrane krvnih sudova, smanjenje količine kolagena u međućelijskoj supstanci i znake hronične inflamacije i angiopatije [24]. U istaživanju Garbera i sar. utvrđeno je da je reparatorni odgovor u pulpi dijabetičnih pacova bio kompromitovan, što je dovelo do hronične inflamacije i redukovanog stvaranja dentinskog mosta [25]. Studije na ćelijskom nivou su pokazale da su u dijabetičnoj pulpi povećane koncentracije medijatora i enzima inflamacije, kao i parametri oksidativnog stresa, što ukazuje na povećani nivo slobodnih radikala u dijabetičnoj pulpi u poređenju sa zdravom [26, 27]. Ilić i sar. su analizirali ljudsku dijabetičnu pulpu i uočili značajne promene u nivoima VEGF i BMP-2, FR značajnih za reparatorni odgovor pulpe [28].

VEGF je od velikog značaja za mikrocirkulatorni sistem zubne pulpe. Ekspresija VEGF i njegovih receptora je identifikovana u tkivu pulpe metodom lančane reakcije polimeraze (PCR) [29, 30] kao i imunohistohemijski [31]. Povećana ekspresija VEGF utvrđena je u nekim patološkim stanjima zubne pulpe kao što su zapaljenje povreda i hipoksija [32-34].

BMP-2 je FR sa značajnom ulogom u funkciji zubne pulpe. Ekspresija BMP-2 u zubnoj pulpi je dokazana imunohistohemijski [35] i PCR metodom [9, 36]. Ovaj FR je odgovoran za diferencijaciju odontoblasta iz pulpnih stem ćelija i za povećanu sekretornu aktivnost odontoblasta u primarnoj, sekundarnoj i tercijarnoj dentinogenezi [37, 38].

Promene u nivoima ovih faktora rasta mogle bi biti od posebnog interesa kada se analiziraju efekti DM na reparatorni odgovor pulpe, imajući u vidu njihov značaj za regulaciju ovog procesa. Njihovi promenjeni nivoi tokom DM mogu izazvati neadekvatnu reakciju zubne pulpe na štetne nadražaje. Ovo je u saglasnosti sa istraživanjem Garbera i sar. [25], koji su utvrdili da DM ugrožava reparaciju zubne pulpe na animalnom modelu pacova, ali i sa empirijski poznatom činjenicom da su reakcije dijabetične pulpe na proceduru prekrivanja pulpe vrlo nepredvidljive.

ZAKLJUČAK

Klinička dilema da li sprovesti postupak prekrivanja pulpe ili proširiti indikacije za pulpektomiju kod pacijenata sa kompromitovanin opštim stanjem usled DM i dalje postoji. Bazični fiziološki pokazatelji i na dokazima zasnovani klinički podaci o ovom problemu su oskudni. Trebalo bi sprovesti opsežna istraživanja o ćelijskim i molekularnim mehanizmima reparatornog odgovora pulpe tokom DM. Zato je neophodno uvek sa oprezom pristupati terapijskim procedurama u cilju očuvanja vitaliteta zubne pulpe kod osoba obolelih od DM.

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