Biolog. Journal of Armenia, 1 (69), 2017

NEW APPROACHES TO ENHANCE HYDROGEN PRODUCTION FROM GLYCEROL BY *ESCHERICHIA COLI*

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Glycerol as a waste material of biodiesel and other industries can be considered for biological hydrogen (H_2) production. Upon *Escherichia coli* glycerol fermentation formate, ethanol and etc. are produced. Formate decomposition by fromatehydrogenaselyase enzymes lead to H_2 and CO_2 formation. Four [NiFe] Hydrogenase (Hyd) enzymes are involved in this process for activity of which heavy metals can be required.The results obtained identify the conditions when reductive conditions has essential role for H_2 production in *E. coli* upon glycerol fermentation. Moreover, mixed carbons or addition of some heavy metal ions enhance H_2 generation. These approaches might be applied to regulate H_2 metabolism upon bacterial industrial wastes (glycerol) fermentation resulting enhanced H_2 production.

Escherichia coli; H_2 production, oxidation-reduction potential; hydrogenase enzymes; glycerol/formate fermentation

Գլիցերոլը որպես կենսադիզելի և այլ արտադրությունների թափոն կարող է հաջողությամբ կիրառվել կենսաջրածնի (H_2) ստացման համար: *Escherichia coli*-ին գլիցերոլի խմորման ժամանակ արտադրոում է մրջնաթթու, էթանոլ և այլ վերջնանյութեր: Մրջնաթթու ջրածինլիազ ֆերմենտը մրջնաթթուն վերածում է մինչև H_2-ի և CO_2-ի: Չորս [NiFe] հիդրոգենազ (Հիդ) ֆերմենտներ, որոնց ակտիվության համար մետաղներ են անհրաժեշտ, մասնակցում են այդ գործընթացին: Ստացված տվյալները վկայում են, որ վերականգնված ռեդօքս պոտենցիալով միջավայրը էական է գլիցերոլի խմորման ընթացքում *E. coli* -ի H_2 արտադրության համար: Խառը ածխածնի աղբյուրները և որոշ ծանր մետաղներ խթանում են H_2-ի արտադրությունը: Այս մոտեցումները կարող են կիրառվել H_2-ի նյութափոխանակության կարգավորման նպատակով և կնպաստեն արդյունաբերական թափոններից (գլիցերոլից) կենսաջրածնի ստացման խթանմանը:

Escherichiacoli, H_2 արտադրություն, օսիդավերականգնող ականպոտենցիալ, հիդրոգենազ ֆերմենտներ, գլիցերոլ մրջնաթթու խմորում

Глицерол – отход биодизельного и других производств может быть успешно использован для получения биоводорода (H_2). В процессе брожения глицерола *Escherichia coli* выделяет муравьиную кислоту, этанол и другие конечные продукты. Фермент формиат водород лиаза трансформирует муравьиную кислоту до H_2 и CO_2. Четыре [NiFe] гидрогеназы, для активации которых необходимы ионы металлов, участвуют в этом процессе. Полученные результаты свидетельствуют о том, что среда с восстановленным редокс потенциалом существенна при брожении *E. coli* для производства H_2. Данные подходы могут быть применены для регулирования метаболизма H_2 у бактерий *E. coli*, содействуя промышленному получению биоводорода из отходов (глицерола).

Escherichia coli, производство H_2, окислительно-восстановительный потенциал, ферменты гидрогеназы, брожение глицерол/муравьиной кислоты

Molecular Hydrogen (H_2) is being recognized as an energy alternative for the future. It is clean, renewable with high energy content, as the energy dismissed upon its combustion (~142 kJ g^{-1}) is ~3.5 fold greater than oil [1, 9, 10]. Dark fermentation is considered as one of the most favored technologies for H_2 production with a great potential for commercialization in the near future. In this respect, genetically and metabolically easy manipulating bacterium *Escherichia coli*,performing dark fermentation andleading to H_2

formation is good candidate to refer for biotechnological proposes [9, 10]. Moreover, the use of cheap substrates (agricultural and food industry wastes) rich of nutrients can be used for H_2 production. This will lead to low-priced H_2 generation with immediate waste treatment [2, 7]. In this regard, glycerol which is commonly recognized as an industrial significant waste, can be used as carbon source by bacteria for H_2 and other valuable chemical compounds production [2, 9].

H_2 is produced from formate, the end product of glycerol or sugar (glucose) fermentation of *E. coli*, by formate dehydrogenase H (FDH-H) and hydrogenase (Hyd) enzymes [4, 8, 10]. In *E. coli* possessesfour [Ni-Fe]-Hyd enzymes encoded by *hya, hyb, hyc, hyf* operons, respectively.For functioning of Hyds and FDH-H heavy metals Ni and Fe and Mo, respectively, are involved and make available pathways for proton and electron transfer during H_2 formation or oxidation [4, 5, 8]. The operation direction (H_2 formation or oxidation) of Hyd enzymes is depends onmany factors, such as carbon (glycerol or glucose) source, pH of the growth medium, etc.: it was stated that Hyd-1 and Hyd-2 function in H_2 oxidation upon glucose and H_2 production modes upon glycerol fermentation [4, 9, 10]. The optimal activity of Hyd-1 was detected under anaerobic conditions, at acidic pH and in the presence of formate, whereas Hyd-2 was at more reduced environment and alkaline pH[4,9,10].

Direct effect of metals on Hyd enzyme activity was also proposed, as the addition of Fe^{2+} affected H_2 production rate by *E. coli in vivo*and increased it *in vitro* at pH 6.5 and pH 7.5 during glycerol fermentation [11]. On the other hand, formate is considered a rich-energy compound as the oxidation and reduction potential of the formate: H_2 couple is very reduced (-420 mV) [12, 13], can be additional energy source during energy restricted (fermentative) conditions [5]. *E. coli* produces and initiallysecretes formateout of the cells to prevent acidification of the cytoplasm. When the drop of bacterial growth pH is accrued, formate is re-imported into the cell trough formate channel FocA and metabolized [5]. Pyruvate formatelyasedirectly interacts with the FocA and regulatesformate translocation. It was proposed that the *hyc* operon is regulated solely in response to formate concentration at low pH. Moreover, formate in flux may result the destruction of Δp, therefore the control of formate metabolism is very important [5,10,12].

The metabolism of bacteria is known to be a set of redox processes affecting ORP. ORP drop (down to -550-600 mV) during anaerobic growth of bacteria in the absence of external electron acceptors has been well-established [12, 13]. ORP is proposed to be valuable for monitoring changes in the metabolic state of bacterial cultures in biotechnology and for optimizing yield of fermentation yields, and has been shown can be useful to discriminate between bacterial species [13].

Thus, many factors such as different ORP, mixed carbon (formate and glycerol) and heavy metal ions (involved in redox reactions of FHL system) influence on bacterial growth and particularly H_2 metabolism are investigated and discussed in the present work.

Determination of *E. coli* batch culture oxidation reduction potential and H_2. H_2 production by bacteria is determined by various qualitative and quantitative methods [12, 13]. It might be determined by chemical reaction of color disappearance during interaction of potassium permanganate ($KMnO_4$) solution in sulfur acid (H_2SO_4) with H_2 [18]. Chemical detection and gas chromatography of H_2 require gas extraction and calculation of its solubility in an aqueous medium. The use of a couple of oxidation-reduction (for example, platinum (Pt) and titanium-silicate (Ti-Si)) electrodes measuring ORP has certain advantages. In contrast to Pt, Ti-Si electrode readings are not affected by the presence of H_2 (or oxygen) in the medium; this allows differentiation of H_2 in the growth and assay medium under anaerobic conditions [12,13].Transformation of ORP data into quantity (concentration) of H_2 expressed in mol/L [13].

Oxidative and reductive routes of glycerol fermentation by *Escherichia coli* batch cultures and their regulation by oxidizing and reducing reagents. ORP critical role in *E. coli* growth in anaerobic conditions [12,13] means that various oxidizers and reducers affecting ORP can mediate growth of bacteria. ORP kinetics and H_2 production was measured in bacterial batch cultures by the difference of pair of redox Pt and Ti-Si electrodes readings [6]. An impermeable oxidizer $K_3[Fe(CN)_6]$ (1 mM) and reducers DTT (3 mM) and dithionite (1 mM) were implemented for application of ORP initial positive (+235±10 mV) and negative (-250±10 mV) values to bacteria, respectively. In the presence of $K_3[Fe(CN)_6]$ *E. coli*growth at different pHs was inhibited resulting in decrease of ORP only to 130±5mV at the log growth phase[6]. In this conditionORP positive or less negative may oxidize thiol groups on bacterial surface and affect on membrane transport and enzymes like F_0F_1 or TrkA under anaerobic conditions, leading to low activity of key enzymes in bacterial fermentation metabolism [10].

Table 1. The effects of reducers on H_2 yield by *E. coli* BW25133 during growth under glycerol fermentation at different.

Growth medium pH	H_2 yield, mol/L		
	Control	Reducers	
		DTT[c]	Dithionite[b]
5.5	0,10±0.01 [a]	0.80±0.04 [c]	ND [d]
6.5	0.73±0.02 [a]	1.30±0.04 [c]	ND
7.5	0.70±0.03 [a]	1.40±0.05 [c]	2.00±0.05 [c]

[a]bacterial culture was of ~8 h growth; [b]3 mM DTT, 1 mM dithionite were added into the growth medium; [c]bacterial culture was of ~3-4 h growth; [d] ND: not determined.

In order to carry out the metabolic processes efficiently, it is very important to maintain the intracellular environment in the reducing state. However, membrane-permeating reducing reagents DTT and dithionite, reducingORP to negative values (-280±12 mV), inhibited the growth of *E. coli* during glycerol fermentation in a concentration-dependent manner [6]. Obviously, extreme reducing conditions may lead to instability in the metabolism. Besides, it was stated, that upon glycerol fermentation DTT at different pHs and dithionite but not oxidizer at pH 7.5 stimulated ~2-3 fold H_2 production in the log growth phase (Table 1). Similar effect with DTT was observed previously during glucose fermentation in *E. coli* [13]. Probably, the reduced environment might lead to formate concentration increase which then can be source for H_2 and CO_2 [6]. It should be noted that because of instability of this reagent in acidic environment effect of dithionite on bacteria was investigated only at pH 7.5.

***Escherichia coli* hydrogen production in batch culture upon formate alone and with glycerol co-fermentation.** To understand the effect of formate on growth in batch culture, H_2 production at different pHs (5.5-7.5) during glycerol fermentationin *E. coli* and Δ*hyaB,* Δ*hybC,* Δ*hycE,* Δ*hyf G*hydrogenase mutantswith deletions of different key subunits of Hyd-1 to 4, respectively, were investigated and main experiments are illustrated in Fig. 1 [12].10 mM formate ~2 fold and 30 or 50 mM formate, completely inhibited wild type growth during glycerol fermentation atpH 5.5, whereas at pH 7.5 and 6.5 formate in the

same concentrations stimulated or had no effect on bacterial growth [12]. So in other experiments when needed 10 mM formate was supplemented to the growth medium.

From the beginning of the lag growth phase the drop of Pt and Ti-Si electrodesform positive to negative values was detected in wild type upon glycerol or formate alone or their combined conditions, pH6.5 (Fig. 1,a). H_2 formation was observed in wild type with the yield of 0.75 ± 0.03 mmol/L at the end of log growth phase, formate supplementation lead to 0.83 ± 0.05 mmol/LH_2 generation at early log phase, which was stimulated ~1.1 fold upon formate and glycerol co-supplementation at pH 6.5 (Fig. 1,a). The same stimulating effect by formate or in combination with glycerol was observed at pH 7.5 [12].Increased, 1.45 to 2.2 ±0.05 mmol/LH_2 production was detected during growth of *hyaB* mutant upon all substrates combinations utilization at pH 6.5 and formate alone at pH 7.5, except upon glycerol only fermentation at pH 7.5 at the beginning of log growth phase. Note, H_2 was not produced in *hycE* (with defective Hyd 3) mutant. H_2 was also produced in *hybC* (with defective Hyd2) mutant during glycerol fermentation at pH 6.5 with the yield of 0.8 ± 0.05 mmol/L, and again stimulated ~1.2 fold to ~1.3 fold during formate alone or with glycerol combination (Fig 1,b).Thus, in the cells grown both with external formate and glycerol H_2 production was stimulated [12]. This stimulation was not pH dependent. The effect can be contributed to Hyd 3 increased activity upon bacterial glycerol fermentation.

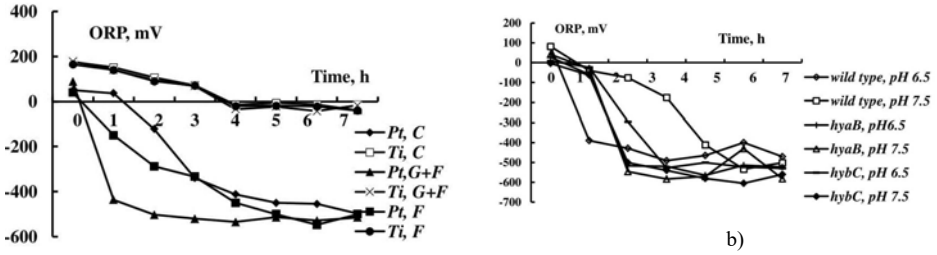

Fig. 1. The kinetics of ORP by *E. coli* BW25113 and Hyd mutants during co- fermentation of10 g/l glycerol (G) and 10 mM formate (F). a) Only *E. coli* BW25113 ORP kinetices are presented, pH 6.5; control (C) was ORP kinetics in the medium with 10g/l glycerol; b) The ORP kinetics by *E. coli* wild type and Hydmutants at pH 6.5 and pH 7.5.

Enhancements of *Escherichia coli*hydrogen productionbyheavy metal ions and their mixturesduring glycerol fermentation.In the study [11] *E. coli* growth was followed during 10 g/Lglycerol batch culture fermentation at pH 5.5 to pH 7.5 in the presence of various heavy metal ions with different oxidation states, as Ni^{2+}, Fe^{2+} or Fe^{3+}, Mo^{6+} and their mixtures at various concentrations. It is worth to mention that the metal ions concentrations were used relaying on the results for *E. coli* and other bacteria [4, 5, 11]. H_2 production yield was 0.75±0.02 mmol H_2/L at 12 h growth of *E. coli* at pH 6.5 during glycerol fermentation, and it was noticeably stimulated (1.9 to 3 fold) in the presence of mixtures of Ni^{2+}+Fe^{3+}, Ni^{2+}+Fe^{3+}+Mo^{6+} or Fe^{3+}+Mo^{6+} (see Table 2).

Table 2.H_2 production yield of *E. coli* BW25113 during glycerol fermentation in the presence of heavy metal ions.

Growth conditions[a]	pH 5.5	pH 6.5	pH 7.5	
	H_2 yield, mmol H_2 L^{-1}	H_2 yield, mmol H_2 L^{-1}	H_2 yield, mmol H_2 L^{-1} (log growth phase)	H_2 yield, mmol H_2 L^{-1} (station growth phase)
Control[c]	0.50±0.02	0.75±0.02	0.75±0.02	0.81±0.02
Ni^{2+}	0.75±0.03 (p< 0.01)[d]	0.71±0.03 (p>0.05)	0.77±0.03 (p>0.05)	1.35±0.01 (p<0.001)
Fe^{2+}	0.60±0.02 (p<0.05)	0.70±0.02 (p>0.05)	0.75±0.02 (p>0.05)	0.83±0.02 (p>0.05)
Fe^{3+}	0.46±0.04 (p>0.05)	0.71±0.04 (p>0.05)	0.72±0.04 (p>0.05)	1.33±0.04 (p<0.001)
Mo^{6+}	0.60±0.03 (p<0.05)	0.75±0.03 (p>0.05)	0.64±0.03 (p>0.05)	0.81±0.03 (p>0.05)
Ni^{2+}+Fe^{3+}	0.70±0.01 (p<0.01)	1.30±0.01 (p<0.001)	0.81±0.01 (p<0.05)	1.35±0.01 (p<0.001)
Ni^{2+}+Fe^{2+}	0.64±0.02 (p<0.025)	0.80±0.02 (p>0.05)	0.80±0.02 (p<0.05	1.36±0.02 (p<0.001)
Fe^{3+}+Mo^{6+}	0.60±0.01 (p<0.05)	2.20±0.01 (p<0.001)	0.75±0.01 (p>0.05)	1.35±0.01 (p<0.001)
Fe^{2+}+Mo^{6+}	0.57±0.03 (p<0.05)	1.40±0.03 (p<0.01)	0.77±0.03 (p>0.05)	1.38±0.03 (p<0.001)
Ni^{2+}+Fe^{3+}+Mo^{6+}	0.77±0.01 (p<0.002)	1.50±0.01 (p<0.01)	0.81±0.01 (p<0.05)	2.24±0.01 (p<0.001)
Ni^{2+}+Fe^{2+}+Mo^{6+}	0.68±0.01 (p<0.01)	0.8±0.01 (p>0.05)	0.83±0.01 (p<0.05)	1.50±0.01 (p< 0.001)

[a]10 g/L glycerol was added into the growth medium; 50 μM Ni^{2+}, Fe^{2+}or Fe^{3+}, 20 μM Mo^{6+}, were supplemented into the growth medium when mentioned; [b] oxidation-reduction potential measured by Pt electrode; [c] control was without metal supplementation; [d] p for difference between the experiment and appropriate control

Similar data were obtained at the certain conditions but at pH 5.5: though the H_2 production yield was ~1.5 fold decreased (0.50±0.02mmol H_2/L) compared with pH 6.5, but metal ions addition again stimulated H_2 yield, particularly ~1.5 fold upon addition of Ni^{2+}alone and Ni^{2+}+Fe^{3+}, Ni^{2+}+Fe^{3+}+ Mo^{6+}or Ni^{2+}+Fe^{2+}+ Mo^{6+} (see Table 2).

Interesting datawith *E. coli*was observed during glycerol fermentation at pH 7.5.Effects of metal ions on H_2 production yield were intense at station growth phase: H_2 production yield was ~1.7 fold stimulated upon all metals (Ni^{2+}, Fe^{3+}, Fe^{2+} and Mo^{6+}) and 2.7-3 fold upon Ni^{2+}+Fe^{3+}+Mo^{6+} mixture supplementations (see Table 2). Some metals have a role in Hyd enzymes biosynthesis and maturation processes, or they might affect enzymes activity [4,5,11].

Concluding remarks.Thus, ORP might one of the physicochemical parameters to take into account for optimizing fermentation processes and developing H_2 production biotechnology.Oxidizers and reducers were used for application of positive and negative ORP values, respectively. Although bacterial growth was repressed upon oxidative and reductive stresses both, the reductive conditions only stimulated H_2 generationupon glycerol fermentation.Externally supplied formate regulatesH_2 production and cell growth in *E. coli* growing on glycerol.Moreover, mixed carbon (co-supplementation of formate with glycerol) might have industrial advantageous application to enhance bio-hydrogen production.Note, responsible Hyd enzymes are relived upon mixed corbon utilization. In addition, some heavy metals (nickel (Ni^{2+}) and iron (Fe^{3+}, Fe^{2+}), molybdenum (Mo^{6+}))

having a role as structural components of Hyd and FDH-H enzymes stimulate bacterial growth and H_2 production upon glycerol utilization.

Consequently, glycerol co-fermentation with organic acids, effects of reducing reagents, heavy metals ions and effective strains could be considered as novel approaches to enhance H_2 in production (Fig. 2).The coupling of H_2 production to utilization of waste materials containing high concentrations of glycerol may same time provide economic and environmental benefits. The results might be taken into account for optimizing fermentation processes on glycerol and developing H_2 production biotechnology.

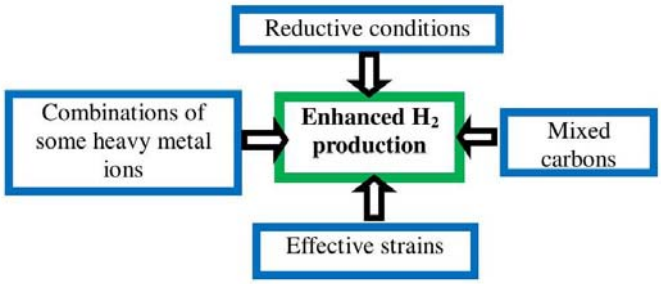

Fig. 2. Approaches to enhance H_2 production by *E. coli* BW25113 during glycerol fermentation.

Acknowledgements

The author thanks to Prof. A. Trchounian (Yerevan State University, Armenia) for voluble comments and discussions. This work was supported by Research grants of State Committee of Science, the Ministry of Education and Science of Armenia, to AT (#13-F002 and 15T-1F123), USA based Armenian National Science and Education Fund grant to AP (NS-biotech-4376 and NS-Microb-3212).

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Biolog. Journal of Armenia, 1 (69), 2017

THE STUDY OF CALCINEURIN ACTIVITY IN PATHOPHYSIOLOGY OF OVARIAN CANCER

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In present study the changes of Ca2+/calmodulin-dependent protein phosphatase calcineurin activity in pathophysiology of ovarian cancer has been investigated. Calcineurin activity has been determined by the spectrofluorimetrically in plasma and tissue samples of the oncologic patients with different stages of disease. Results obtained suggested that, depending on the stage (I, II, III) of disease, calcineurin activity was shown to be increased in the plasma and tumor tissue of ovarian cancer patients. It is necessary to emphasize that changes in calcineurin activity in the pathophysiology of ovarian cancer also depend on tissue differentiation.

Calcineurin - ovarian cancer – inflammation - tissue differentiation

Ներկա աշխատանքում ուսումնասիրվել է Ca^{2+}/կալմոդուլին-կախյալ պրոտեին ֆոսֆատազ կալցինեյրինի ակտիվության փոփոխությունը ձվարանների քաղցկեղի պաթոֆիզիոլոգիայում: Կալցինեյրինի ակտիվությունը որոշվել է հիվանդության տարբեր փուլերում գտնվող քաղցկեղային հիվանդների պլազմայի և հյուսվածքային նմուշներում սպեկտրաֆլուորիմետրիկ եղանակով: Ստացված տվյալները վկայում են, որ, հիվանդության փուլից (I, II, III) կախված, կալցինեյրինի ակտիվությունն աճում է ձվարանների քաղցկեղով հիվանդների պլազմայում և ուռուցքային հյուսվածքում: Հարկ է ընդգծել, որ կալցինեյրինի ակտիվության փոփոխությունը ձվարանների քաղցկեղի պաթոֆիզիոլոգիայում կախված է նաև հյուսվածքային դիֆերենցիացիայից:

Կալցինեյրին – ձվարանների քաղցկեղ – բորբոքում – հյուսվածքային դիֆերենցիացիա

В настоящей работе было изучено изменение активности Ca2+/кальмодулин-зависимой протеин фосфатазы кальцинейрина при патофизиологии рака яичников. Активность кальцинейрина была определена спектрофлуориметрически в образцах плазмы и ткани онкологических больных с различными стадиями заболевания. Полученные данные показали, что активность кальцинейрина в зависимости от стадии (I, II, III) заболевания увеличивается в плазме и опухолевой ткани больных с раком яичников. Необходимо подчеркнуть, что изменения активности кальцинейрина при патофизиологии рака яичников также зависят от дифференциации тканей.

Кальцинейрин – рак яичников – восполение – дифференциация тканей