African Journal of Biotechnology Vol. 7 (25), pp. 4843-4849, 29 December, 2008
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2008 Academic Journals

Review

Properties of glucoside 3-dehydrogenase and its potential applications

Li-Qun Jin and Yu-Guo Zheng*

Institute of Bioengineering, Zhejiang University of Technology, Hangzhou, 310014, Zhejiang Province, People's Republic of China.

Accepted 1 December, 2008

Glucoside 3-dehydrogenase, one of the glucose redoxidases, is perhaps known for the vital role it plays in converting a series of sugars to their corresponding 3-ketoglucosides. Glucoside 3-dehydrogenase has attracted considerable attention in recent years due to broad substrate specificity and excellent regioselectivity. Glucoside 3-dehydrogenase is a FAD-enzyme, which is capable of oxidizing glucosides and galactosides to their corresponding 3-ketoglycosides, due to the enzyme's site-selective oxidation of the C-3 hydroxyl group. These 3-ketoglucosides are useful as building blocks for chemicals such as detergents and polymers. The versatile glucoside 3-dehydrogenase has potential applications in different fields including sugar industry, clinical diagnosis and pharmaceutical intermediates synthesis. This review attempts to describe the glucoside 3-dehydrogenase concerning the sources, properties and applications in detail.

Key words: Glucoside 3-dehydrogenase, application, 3-ketoglucoside.

INTRODUCTION

In the course of studies on carbohydrate metabolism of *Agrobacterium tumefaciens* IAM 1525, D-Glucoside 3-dehydrogenase (G3DH) was first identified and purified in the 1960s, which was later investigated and discovered in other organisms (Fukui and Hayano, 1969; Hayano and Fukui, 1967; Chern et al., 1976). G3DH is a flavine adenine dinucleotide (FAD)-enzyme which oxidizes glucosides and galactosides at C-3 position to their corresponding 3-ketoglycosides and transfers electrons from glycosides to terminal oxidase via cytochrome. Interestingly, the enzyme could react with various artificial electron acceptors such as 2,6-dichlorophenolindophenol (DCPIP), phenazine methosulfate, and ferricyanide *in vitro* (Takeuchi et al., 1988a; Chen et al., 2003; Chern et al., 1976). Various glucose oxidoreductases have been reported and utilized for the enzymatic determination of glucose. Among them, only few enzymes that oxidize hydroxyl group of pyranose and its derivatives at C-3 position have been reported. To date, many literatures indicate that enzymatic conversion of sugars and their derivatives with G3DH are of interest for carbohydrate chemistry and technology due to the enzyme's site-selective oxidation of the C-3 hydroxyl group (Fukui and Hayano, 1969; Hayano and Fukui, 1967; Kojima et al., 1999; Maeda et al., 2003; Stoppok et al., 1992).

3-Ketoglycoside, the enzymatic conversion product of G3DH, is a potential raw material for commodity chemicals such as polymers and surfactants because the keto group has reactivity different from that of the hydroxyl (Maeda et al., 2003). G3DH exhibits extremely broad substrate specificity and regioselectivity. It was interesting to access new 3-keto sugars through G3DH (Pietsch et al., 1994; Stoppok et al 1992; Zhang et al., 2005). Moreover, the G3DH can be applied for the measurement of 1,5-anhydro-D-glucitol (1,5-AG) as a clinical marker of diabetes (Kojima et al., 1999), and for the production of glucosidase inhibitor medicament with microbial method. As a result, the G3DH has evoked substantial attention and it is becoming more and more demanding. Here, we attempt to describe the G3DH concerning the sources, properties and applications in detail.

MICROORGANISMS PRODUCING GLUCOSIDE 3-DEHYDROGENASE

To the best of our knowledge, G3DH is found both in bacterium and fungi. G3DH was first identified in *Agro-*

*Corresponding author. E-mail: zhengyg@zjut.edu.cn. Tel: +86-571-88320379. Fax: +86-571-88320630.

Table 1. The properties of the enzyme from various sources.

Souces	Molecular weight(kDa)	Optimal pH (for DCPIP)	Isoelectric point	K_m (for glucose)	Existence state	Synthesis way	inhibitor
A.tumefaciens	68	6.0-6.7	ND	0.16 mM	Solube protein	Inducible	Ca^{2+}, Cu^{2+}
S.Maltrophilia	66	6.0-7.0	ND	1.1 mM	Solube protein	Constitutive	Cu^{2+},Ag^{2+},Hg_2Cl_2
F.saccharophilum	270(MB), 66 (WS)	6.0	ND	0.12 mM (MB); 0.11 mM (WS)	Membrane-binding and soluble protein	ND	Hg^{2+},p-chloromercuribenzoate
A. bisporus	55	4.5*	3.6	1.83 mM	Solube protein	Inducible	ND
C.marinoflava	67	8.0	ND	1.5 mM	Membrane-binding protein	ND	ND
Halomonas(Deleya)	67	ND		ND	Soluble protein	Inducible	ND

Note: ND represents no detected; MB represents the membrane-banded enzyme; WS represents the water-soluble enzyme; VAA represents validoxylamine A ; DCPIP represents 2,6-dichlorophenolindophenol; 4.5* represents the optimal pH for p-benzoquinone.

bacterium tumefaciens, a plant tumor inducing bacterium, in the study of carbohydrate metabolism (Hayano and Fukui, 1967). It was found that G3DH played an important role and 3-ketoglycosides were the first intermediates in the metabolic pathway of carbohydrate. Then, 3-ketoglucosides were further hydrolyzed to liberate 3-ketoglucose by 3-ketoglucosidase and to glucose-3-ketoglucose by reductase (Hayano and Fukui, 1967; Tsugawa et al., 1998). More noticeably, the two functions of G3DH for transport reaction was put forward by Chern et al. (1976), as a member of the energy-supplying system and as an effector on maintenance of membrane structure being proper status for transport reactions. From then on, several microorganisms harboring G3DH activity have been screened. The enzyme was discovered in *Flavobacterium saccharophilum* when Asano et al. (1984) attempted to elucidate the degradation process of validamycins A. With the development of the enzyme, an upsurge of study has been taking place in China as well.

Some institutes and universities have taken part in this research in recent years. During the study of validamycin A degradation, Zhang et al. (2006) and Zheng et al. (2005) in our laboratory also discovered the G3DH in *Pseudomonas* sp. HZ519 and in *Stenotrophomonas maltrophilia* CCTCC M 204024, respectively. It was suggested that the enzyme was of great importance in the degradation pathway of validamycin A. First, validamycin A was hydrolyzed to D-glucose and validoxylamine A. Then, validoxylamine A was degraded to 3-ketovalidoxylamine A by G3DH. Further, 3-ketovalidoxylamine A was degraded to validamine, valienamine, and unsaturated ketocyclitols by other lyase (Takeuchi et al., 1985; Zhang et al., 2006; Zheng et al., 2005). Additionally, Tsugawa et al. (1996, 1998) also discovered the G3DH from a marine Gram-negative bacterium *Halomonas (Deleya)* SP. α-15 and from *Cytophaga marinoflava* IFO 14170. Bacteria as well as fungi provided excellent source of G3DH. The G3DH was first reported in fungi of mushroom (*Agaricus bisporus)* by Morrison et al. (1999) and was purified from liquid cultures of the basidiomycete *A. bisporus* after growth with D-cellobiose or D-glucose as carbon source. So far, only few of microorganisms were successfully screened.

THE PURIFICATION AND CHARACTERIZATION OF GLUCOSIDE 3-DEHYDROGENASE FROM MICROORGANISMS

Some organisms producing G3DH were purified and characterized. The properties of G3DH from different organisms have been demonstrated as shown in Table 1. Many studies clearly indicated that the G3DH can be purified from membrane as well as soluble fraction; the G3DHs of *A. tumefaciens*, *Halomonas* (*Deleya* sp), *S. Maltrophilia* and *A. bisporus* are soluble enzymes. However, the enzymes of *A. tumefaciens*, *Halomonas* (*Deleya* sp.) and *S. Maltrophilia* are periplasmic soluble protein isolated in active holo form; the enzyme of *A. bisporus* is extracellular. It was found that the G3DH is a membrane-binding protein and composed of a single peptide with a molecular mass of 67 kDa in *C. marinoflava* (Tsugawa et al., 1996). In *F. saccharophilum*, the G3DH existed both in the membrane fraction and in the soluble fraction with a molecular mass of 270 and 66 kDa, respectively. 80% of the enzyme is in the mem-

brane fraction, consisting of four subunits each with a molecular mass of 66 kDa (Takeuchi et al., 1988b, 1986).

According to the literature, the G3DH can be prepared according to different methods. Takeuchi et al. (1986) reported the purification process of G3DH from *F. saccharophilum*. The membrane-bound enzyme was first solubilized by triton X-100 and purified about 280-fold with an overall yield of 30% by column chromatography on DEAE- and CM-Sepharose CL-6B and gel filtration on Sephacryl S-300. Takeuchi et al. (1988b) also introduced a simple method to purify the soluble G3DH from *F. saccharophilum*. Hayano and Fukui (1967) took five steps to purify the G3DH about 126-fold with a yield of 12.3% from *A. tumefaciens* by three steps of ammonium sulfate fraction and two steps of DEAE-cellulose column chromatography (Hayano and Fukui, 1967). More recently, the soluble G3DH from *S. maltrophilia* was also purified about 37.4-fold with a yield of 24.7% by column chromatography on High Q IEX and Methyl HIC and High S IEX (Zhang et al., 2006).

It is generally accepted that G3DH exhibited extremely broad substrate specificity and converts sugars them to the corresponding 3-keto sugars. The G3DH from *Halomonas* SP. a-15 strain could react against C-3 the hydroxyl group of mono-, di-, and tri-saccharides. It could utilize monosacchrides such as glucose and galactose; disaccharides such as maltose, lactose; and trehalose, and also α-substituted sugars such as 1,5-anhydro-D-glucitol and methyl-α-D-glucopyraoside. Hamafuji et al. (2002) succeeded in the construction of a novel multi-sugar analysis system with G3DH, employing an enzyme electrode and a sugar separation column. Zhang et al. (2006) also demonstrated that the G3DH of *S. Maltrophilia* has high activity toward D-glucose, α-methyl-D-glucoside, cellobiose, sucrose, trehalose, maltose, lactose, validamycin A, validoxylamine A, acarbose, 2-Deoxy-D-glucose and galactose. Moreover, it was found the G3DH from *A. tumefaciens* is reactive with hexose, D-glucose and D-galactose, while D-fructose, D-mannose and D-allose are not reactive with the enzyme (Hayano and Fukui, 1967). Morrison et al. (1999) demonstrated that the G3DH of *A. bisporus* could oxidize a wide range of sugars, such as D-glucose, D-cellobiose, D-maltose, L-arabinose and sucrose. Nevertheless the enzyme from *A. bisporus* has a much lower specificity with sucrose than the bacterial G3DH. However, the enzymatic conversion product of trehalose by G3DH of *F. saccharophilum* is not similar to that of *Halomonas*. The product of *F. saccharophilum* is 3-ketotrehalose, which was formed by the oxidation of one of the third hydroxyl groups of a-D-glucopyranoside in trehalose; and the latter is not 3-ketotrehalose but 3,3'-diketotrehalose, in which both third hydroxyl groups of glucopyranosides are oxidized (Sode et al., 2001). This would explain the difference in the substrate specificity between G3DH from various organisms.

As the enzyme is called D-Glucoside 3-dehydrogenase, it is generally accepted that D-glucose had the highest affinity to the G3DH with the lowest K_m values. The K_m values of G3DH from *F. saccharophilum* for validoxylamine A and D-glucose were 1.1 and 0.12 mM, 0.63 and 0.11 mM, for the membrane-binding enzyme and for the soluble enzyme, respectively (Takeuchi et al., 1988b, 1986). However, the K_m values of G3DH from *S. Maltrophilia* for validoxylamine A and D-glucose were 8.3 and 1.1 mM, respectively (Zhang et al., 2006), which was about 10 times more than the K_m value of *F. saccharophilum*. The K_m values of G3DH for D-glucose from *A. tumefaciens*, *A. bisporus* and *C. marinoflava* were 0.16, 1.83 and 1.5 mM, respectively (Hayano and Fukui, 1967; Morrison et al., 1999; Tsugawa et al., 1996).

FACTORS AFFECTING THE ACTIVITY OF GLUCOSIDE 3-DEHYDROGENASE

Numerous factors, such as the inducer, pH and metal ions, turn out to affect the activity of G3DH. G3DH is generally inducible, with a few of them being constitutive. Namely, most of the enzyme activity could be detected only in the presence of suitable inducers. Studies indicated the G3DHs of *A.tumefaciens, Halomonas* (*Deleya* sp) and *A. bisporu*s were all inducible enzymes. The enzyme of *Halomonas (Deleya* sp.) could be induced by α-methyl-D-glucoside, lactose, and isopropylthiogalactopyranoside (Kojima et al., 1999). However, the enzyme of the mushroom (*A. bisporus*) was induced by cellobiose, and it took more than 12 weeks for *A. bisporus* to grow and produce this enzyme (Morrison et al., 1999), which is different from that of *Halomonas*. In this case, soluble G3DH is more desirable because of the costly revulsants. Unlike other organisms, the enzyme from *S. Maltrophilia* was soluble and constitutive, which will promote the application prospect of the G3DH (Zhang et al., 2006).

It is obvious that pH significantly affects the enzyme activity. The enzyme exhibits comparatively high activity at the optimum pH than at too acidic or alkaline environment. The optimum pH of G3DH was distinct with different artificial electron acceptors. The optimal pH of G3DH from *F. saccharophilum* for DCPIP, phenazine methosulfate, and purified cytochrome C_{551} reductase activity were 6.0, 8.0~9.0 and 7.0, respectively (Takeuchi et al., 1988b). The optimal pH of G3DH from *S. maltrophilia* and from *A. tumefaciens* is similar in the range of 6.0-7.0 and 6.0-6.7 at the DCPIP as the artificial electron acceptors, respectively (Hayano and Fukui, 1967; Zhang et al., 2006). However, the optimal pH of G3DH from *A. bisporus* was 4.5 for *p*-benzoquinone, showing an acidophilic property (Morrison et al., 1999). Moreover, the enzyme from a marine bacterium *C. marinoflava* could react under high salinity; the optimum pH was around 8.0, showing a typical property of marine bacterial enzymes (Tsugawa et al., 1996).

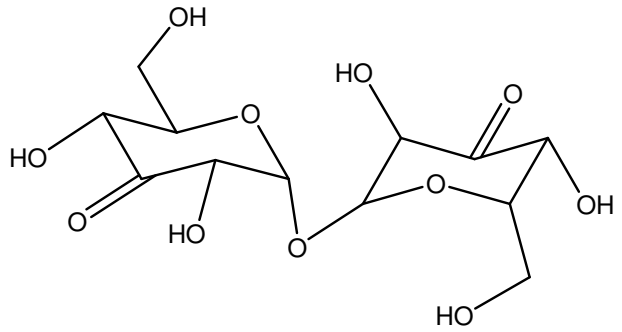

Figure 1. Structure of 3, 3'-diketotrehalose.

As far as G3DH is concerned, effect of metal ions on the enzyme activity in many investigations indicated that Cu^{2+}, Ca^{2+} and Hg^{2+} all affect the activity of the G3DH. On one hand, the G3DH activity of *A. tumefaciens* was almost completely inhibited by Ca^{2+} at a concentration of 1 mM and strongly inhibited by Cu^{2+}. On the other hand, the Ca^{2+} did not inhibit the enzyme activity of *S. maltrophilia* and the Cu^{2+} did not inhibit the G3DH activity of *F. saccharophilum*. The G3DH activity of *S. maltrophilia* was completely inhibited by Cu^{2+}, Ag^{2+} and Hg_2Cl_2. Besides, the G3DH activity of *F. saccharophilum* was completely inhibited by Hg^{2+} (Kurowshi et al., 1975; Takeuchi et al., 1988b; Zhang et al., 2006).

APPLICATIONS OF GLUCOSIDE 3-DEHYDROGENASE

Recently, much attention has been paid to the microbial transformation of glucose or glucose-containing disaccharides to the corresponding 3-ketosaccharides for application in the chemical industry, clinical diagnose and pharmaceutical intermediates. In fact, the study of the applications of G3DH is receiving considerable attention. Some have been successfully applied to industrial production; meanwhile, some are under active development.

Sugar chemical industry

Biosynthesis of 3-keto sugars by G3DH provides a feasible and valuable route provided the G3DH exhibited extremely broad substrate specificity and regioselectivity. Sugars such as disaccharides, although available on a ton scale in high purity and for a reasonable price, are not yet being used on a large scale as chemicals. The main reason is that they possess some hydroxyl groups with similar reactivity, and this makes their utilization difficult. Therefore, if one of the groups can be transformed to a more reactive group, a process for utilizing them would be easily constructed. More importantly, since the 3-keto sugars cannot conveniently be synthesized, their production by the one-step enzymic route is of much interest. Additionally, the application of G3DH for the production of 3-keto-sugars provides favorable conditions for the transfer of the reaction to a technical scale. By virtue of these obvious advantageous, it is interesting to prepare new 3-keto sugars through G3DH catalyzing the oxidation of the C-3 hydroxyl group. The 3-keto sugars not only are potential raw materials for carbohydrate-based products because the keto group has reactivity different from that of the hydroxyl but also are useful for producing a number of compounds, including aminoglycosides antibiotics, sugar polymers, food additives and antioxidants (Fukui and Hayano, 1969; Maeda et al., 2001; 2003; Schuerman, 1997; Stoppok et al., 1992). For instance 3-ketosucrose, obtained from sucrose via G3DH, was shown to be an appropriate and versatile synthon for regioselective syntheses (Pietsch et al., 1994; Simiand et al., 1995).

In recent years, G3DH used in sugar analysis had also been put forward (Hamafuji et al., 2002; Pothukuchy et al., 2006). Sugar analyses based on enzyme reaction have been widely utilized in food processing, fermentation control, and also in clinical diagnostics, considering the substrate specificity of the enzyme reaction. Hamafuji et al. (2002) constructed an amperometric enzyme electrode employing G3DH and also developed a multi-sugar analysis system combined with the G3DH sensor and sugar analysis chromatography. The system could discriminate the four components of glucose, 1,5-anhydro-D-glujcitol, trehalose, and N-carbamoyl-β-D-glucopyranosylamine.

Trehalase inhibitor

3,3'-diketotrehalose (3,3'dkT, Figure 1) is the product of G3DH enzymatic conversion, a novel trehalose derivative, in which both third hydroxyl groups of glucopyranosides were oxidized. 3,3'dkT has an inhibitory effect toward pig-kidney and Bombyx mori trehalases (Sode et al., 2001). Trehalase (EC 3.2.1.28) specifically hydrolyzes trehalose into two glucose molecules. In insects, the use of sugar as an energy source is controlled by trehalase. Trehalase is the rate-limiting enzyme in the process of glycogen synthesis from hemolymph trehalose in developing ovaries of the silkworm (Jorge et al., 1997; Zheng et al., 2004). Hence this enzyme may be regarded as a putative new target for insect control. With the development of the enzymatic method for trehalose production, the utilization of trehalose as the substrate for the enzymatic conversion system based on G3DH is of great value. Many other trehalase inhibitors as validamycin A, validoxylamine A, Salbostain and so on are basically produced by actinomycetes as antibiotics or their derivatives. The G3DH enzyme conversion system for 3,3'dkT production is a one-step route with high yield and the price of trehalose is low. Therefore, despite the lower inhibition of the 3,3'dkT, it is advantageous for large amount dosages, considering its application for insecticides (Sode et al.,

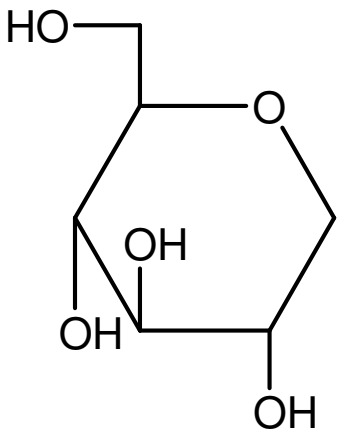

Figure 2. Structure of 1,5-anhydro-D-glucitol.

2001; Zheng et al., 2004). Interestingly, 3,3'dkT is readily converted to the amino derivatives by reductive amination and is valuable as a starting compound for the further development and preparation of several amino sugars. So, this will further promote the application of G3DH (Asano et al., 1989; Sode et al., 2001).

Clinical diagnosis

1,5-anhydroglucitol (1,5-AG) is a major polyol in human blood which has a pyranoid structure (Figure 2). Serum 1,5-AG concentration is normally stable at a constant level about 20-40 µg/ml, but decreases greatly in hyperglycemia. Therefore, 1,5-AG is generally used as a clinical marker of glycemic control in diabetes mellitus patients. Previously, pyranose oxidase-based systems were the most widely utilized method for 1,5-AG diagnosis. However, pyranose oxidase was not highly selective toward 1,5-AG and detection of pyranose oxidase activity also required combination with peroxides (horseradish) to catalyze the color-developing reaction. Furthermore, the enzymatic measurement system utilizing oxidases would be affected by the dissolved oxygen. So it is important to develop a novel serum 1,5-AG assay kit using new enzyme. Some investigations demonstrated that it was advantageous to determine the 1,5-AG level in serum with G3DH. First, the reaction is not affected by dissolved oxygen. Second, the reaction could be measured by a simple color-developing reaction in combination with appropriate artificial electron acceptors. Furthermore, G3DH is highly reactive toward 1,5-AG (Hamafuji et al., 2002; Tsugawa et al., 1996; 1998; Zhang et al., 2006). Depending on these, Hamafuji et al. (2002) constructed a serum 1,5-AG assay kit with G3DH. The reaction is depicted as Figure 3. However, Hamafuji et al. (2002) indicated that the G3DH method clinically for the serum 1,5-AG assay would be preferably applied without any other G3DH substrates interference except of 1,5-AG.

Pharmaceutical intermediates synthesis

In recent years, G3DH has also received considerable attention in the production of glycosidase inhibitor medicament with microbial method. Glycosidase are enzymes used for the cleavage of glycoside bonds and are responsible for glycoprotein processing on the surface of the cell wall and for carbohydrate digestion in animals. Inhibition of these enzymes has significant implications for both antiviral and antidiabetic chemotherapy (Zheng et al., 2005; 2006). The structure of validoxylamine A contains two pseudo-glucose moieties, valienamine and validamine, which display strong glycosidase inhibition activity. Many studies had clearly demonstrated that validoxylamine A is degraded to validamine, valienamine and unsaturated ketocyclitols through 3-ketovalidoxylamine A by G3DH and 3-ketovalidoxylamine A C–N lyase (Figure 4). Moreover, it was found that the G3DH not only facilitated the hydrolysis of validamycin A with β-glucosidase but also determined the yield of valienamine and validamine (Asano et al., 1984; Takeuchi et al., 1985; 1988a; Zhang et al 2005; 2006). That is to say that the production of glucosidase inhibitor of validamine and valienamine directly depended on the amount of G3DH from the organisms. On the other hand, valienamine is a very important chemical intermediate in the synthesis of other pseudo-oligosaccharidic α–gluco-sidases inhibitors, such as acarbose, adiposins, acarviosin, trestatins, voglibose, etc. These pseudo-oligosaccharides exhibit stronger enzyme inhibition activities than valienamine itself (Degwert et al., 1987; Fukase 1997; Furumoto et al., 1992; Ogawa et al 1996; 1988; Xue et al., 2007). So, the production of glucosidase inhibitor by degradation of validamycin A utilizing the G3DH is of great prospect.

CONCLUSIONS

The past decades had witnessed the development of glucoside 3-dehydrogenase; both their properties and applications in manufacture of pharmaceutical intermediates and commodity industry. The enzyme is becoming more and more appreciated by scientists with its site-selective oxidation of the C-3 hydroxyl group and its broad substrate specificity. These substrates have a pyranose ring, as opposed to the furanose ring of D-fructose. It is suggested that the C-1 hydroxyl group, C-2 hydroxyl group and the C-4 hydroxyl group are not necessary for enzymatic activity and the C-3 hydroxyl group is the key substrate for the enzyme.

However, there are only few microorganisms screened that could produce G3DH. Besides, most of the G3DHs belonged to membrane-bounded protein and are inducible enzymes. Thus, they required detergents and revulsants in isolating the enzyme and maintaining their

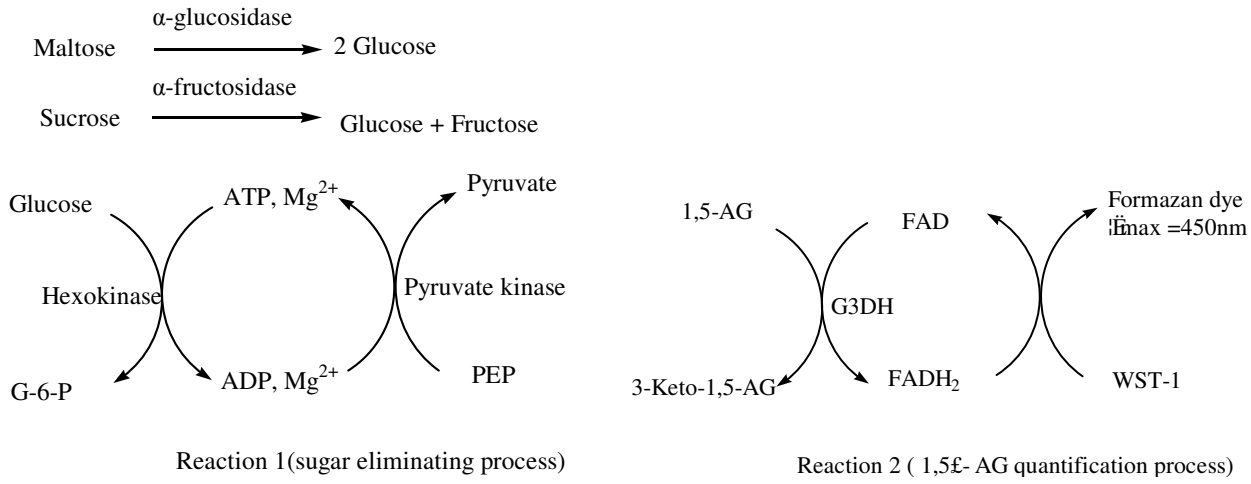

Figure 3. Reaction scheme of 1,5-anhydro-D-glucitol measurement in serum specimen with G3DH.

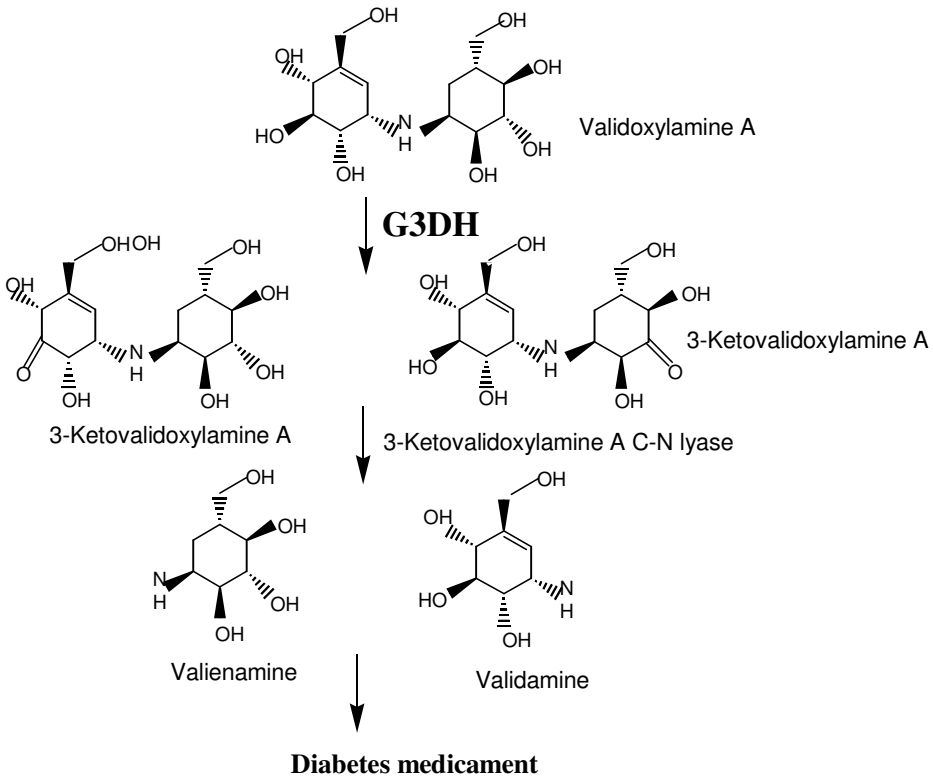

Figure 4. Application of G3DH in diabetes medicament synthesis.

activity, which hindered the broad practical use of the enzyme. So, it is necessary to discover the soluble and constitutive G3DH to broaden its practical use. On the other hand, it is an alternative way applying the engineered strains to promote the higher expression of G3DH. Schuerman et al. (1997) described the cloning of a fragment of DNA from the genome of *A. tumefaciens*, which conferred upon *Eschericia coli* the ability to grow on media containing sucrose as the sole carbon source. The engineered strains could produce higher yield of 3-keto-glycosides and catabolic processes that competed with yield for product could be reduced or eliminated.

It is believed that an increasing number of novel G3DH producing organisms will be screened and their potential

applications in various fields will be further exploited in the near future. Therefore there is a bright and promising future of the enzyme, G3DH.

ACKNOWLEDGEMENTS

This work was supported by the Fund of the National High Technology Research and Development Program of China (863 Program) (No. 2006AA10A209), the National Natural Science Foundation of China (No. 20872132), the R and D Project of Science and Technology of Zhejiang Province (No. 2008C32026).

REFERENCES

Asano N, Katayama K, Takeuchi M, Furumoto T, Kameda Y (1989). Preparation of 3-amino-3-deoxyderivatives of trehalose and sucrose and their activities. J. Antibiot.. 4: 585-590.

Asano N, Takeuchi M, Ninomiya K, Kameda Y, Matsui K (1984). Microbial degradation of validamycin A by *Flavobacterium saccharophilum*: enzyme cleavage of C–N linkage in validoxylamine A. J. Antibiot. 37: 859-867.

Chen XL, Fan YX, Zheng YG, Shen YC (2003). Properties and production of valienamine and its related analogues. Chem. Rev. 103: 1955-1977.

Chern CK, Hayano K, Kusaka I, Fukui S (1976). D-Glucoside 3-Dehydrogenase as a Common factor for various transport reactions in *Agrobacterium tumefaciens,* Agric. Biol. Chem. 40: 2193-2197.

Degwert U, Hulst RV, Pape H, Richard EH, John M, Beal P, Keller JP, Floss HG (1987). Studies on the biosynthesis of the a -glucosidase inhibitor acarbose: valienamine, a m-C_7N unit not derived from the shikimate pathway. J. Antibiot.11: 855-861.

Fukase H (1997). Development of voglibose (Basen R), an antidiabetic agent. J. Synth. Org. Chem. 55: 920-925.

Fukui S, Hayano K (1969). Micro methods for determination of 3-ketosucrose and 3-ketoglucose. Agric. Biol. Chem. 33: 1013-1017.

Furumoto S, Kameda Y, Matsui K (1992). Enzymatic synthesis of glucoside derivatives of validamine and valienamine. Chem. Pharm. Bull. 40: 1871-1875.

Hamafuji T, Takano Y, Tsugawa W, Sode K (2002). Multi-sugar nanlysis system using a novel glucose-3-dehydrogenase electrode, Instrum. Sci. Technol. 30: 97-105.

Hamafuji T, Tsugawa W, Sode K (2002). Clinical application of the serum 1,5-anhydroglucitol assay method using glucose 3-dehydrogenase. J. Clin. Lab. Anal. 6: 299-303.

Hayano K, Fukui S (1967). Purification and properties of 3-ketosucrose formingenzyme from the cells of *Agrobacterium tumefaciens*. J. Biol. Chem. 242: 3665-3672.

Jorge JA, Polizeli MDTM, Thevelein JM, Terenzi HF (1997). Trehalases and trehalose hydrolysis in fungi. FEMS Microbiol. Lett. 154: 165-171.

Kojima K, Tsugawa W, Hamahuji T, Watazu Y, Sode K (1999). Effect of growth substrates on production of new soluble glucose 3-dehydrogenase in *Halomonas* (Deleya) sp. A-15. Appl. Biochem. Biotechnol. 77-79: 827-834.

Kurowski W, Fensom A, Pirt S (1975). Factors influencing the formation and stability of D-glucoside 3-dehydrogenase activity in cultures of *Agrobacterium tumefaciens*. J. Gen. Microbiol. 2: 191-202.

Maeda A, Adachi S, Matsuno R (2001). Improvement of selectivity in 3-ketocellobiose production from cellobiose by *Agrobacterium tumefaciens*. Biochem. Eng. J. 8: 217-221.

Maeda A, Adachi S, Matsuno R (2003). Chromatographic separation of 3-ketoglucose and glucose or 3-ketocellobiose and cellobiose using a cation-exchange resin in potassium-ion form. Biochem. Eng. J. 13: 15-20.

Morrison SC, Wood DA, Wood PM (1999). Characterization of a glucose 3-dehydrogenase from the cultivated mushroom (*Agaricus bisporus*). Appl. Microbiol. Biotechnol. 51: 58-64.

Ogawa S, Ashiura M, Uchiuda C, Watanabe S, Yamazaki C, Yamagishi K, Inokuchi J (1996). Synthesis of potent b - D -glucocrebrosidase inhibitors: N-alkyl-b -valienamines. Bioorg. Med. Chem. Lett. 6: 929-932.

Ogawa S, Ikeda N, Takeda H, Nakagawa Y (1988). Synthesis of some valienamine epoxides: on the structure of the alpha-amylase inhibitor NS-504. Carbohydr. Res.75: 294-301.

Pietsch M, Walter M, Buchholz K (1994). Regioselective synthesis of new sucrose derivatives via 3-keto sucrose. Carbohydr. Res. 254: 183-194.

Pothukuchy A, Mano N, Georgiou G, Heller A (2006). A potentially insect-implantable trehalose electrooxidizing anode. Biosens. Bioelectron. 22: 678-684.

Schuerman PL, Liu JS, Mou H, Dandekar AM (1997). 3-ketoglycoside-mediated metabolism of sucrose in E. coli as conferred by genes from *Agrobacterium tumefaciens*. Appl. Microbiol. Biotechnol. 47: 560-565.

Simiand C, Samain E, Martin OR, Driguez H (1995). Sucrose analogues modified at position 3: chemoenzymatic synthesis and inhibition studies of dextransucrases, Carbohydr. Res. 267: 1-15.

Sode K, Akaike E, Sugiura H, Tsugawa W (2001). Enzymatic synthesis of a novel trehalose derivative, 3, 3'-diketoneo-trehalose and its potential application as the trehalase enzyme inhibitor. FEBS Lett. 489: 42-45.

Stoppok E, Matalla K, Buchholz K (1992). Microbial modification of sugars as building blocks for chemicals, Appl. Microbiol. Biotechnol. 36: 604-610.

Takeuchi M, Asano N, Kameda Y, Matsuin K (1985). Purification and properties of 3-ketovalidoxylamine A C-N lyase from *Flavobacterium saccharophilum*. J. Biochem. 98: 1631-1638.

Takeuchi M, Asano N, Kameda Y, Matsui K (1988a). Physiological role of glucoside 3-dehydrogenase and cytochrome C_{551} in the sugar oxidizing system of *Flavobacterium saccharophilum*. J. Biochem. 103: 938-943.

Takeuchi M, Asano N, Kameda Y, Matsui K (1988b).Purification and properties of soluble D-glucoside 3-dehydrogenase from *Flavobacterium saccharophilum*. Agric. Biol. Chem. 52: 1905-1912.

Takeuchi M, Ninomiya K, Kawabata K, Asano N, Kameda Y, Matsui K (1986). Purification and properties of glucoside 3-dehydrogenase from *Flavobacterium saccharophilum*. J. Biochem. 4: 1049-1055.

Tsugawa W, Horiuchi S, Tanaka M, Wake H, Sode K (1996). Purification of a marine bacterial glucose dehydrogenase from Cytophaga marinoflava and its application for measurement of 1,5-anhydro-D-glucitol. Appl. Biochem. Biotechnol. 56: 301-310.

Tsugawa W, Ogasawara N, Sode K (1998). Fluorescent measurement of 1,5-anhydro-D-glucitol based on a novel marine bacterial glucose dehydrogenase, Enzyme Microb. Technol. 22: 269-274.

Xue YP, Zheng YG, Shen YC (2007). Enhanced production of valienamine by *Stenotrophomonas maltrophilia* with fed-batch culture in a stirred tank bioreactor. Proc. Biochem. 42: 1033-1038.

Zhang JF, Zheng YG, Shen YC (2005). Advance of research on glucoside 3-dehydrogenase. Chin. J. Bioproc. Eng. 3: 14-17.

Zhang JF, Zheng YG, Xue YP, Shen YC (2006). Purification and characterization of the glucoside 3-dehydrogenase produced by a newly isolated *Stenotrophomonas maltrophilia* CCTCC M 204024. Appl. Microbiol. Biotechnol. 71: 638-645.

Zheng YG, Jin LQ, Shen YC (2004) Resin-catalyzed degradation of validamycin A for production of validoxylamine A. Catal. Commun. 5: 519-525.

Zheng YG, Shentu XP, Shen YC (2005a). Inhibition of porcine small intestinal sucrase by valienamine. J. Enzyme Inhib. Med. CHem. 20: 49-53.

Zheng YG, Xue YP, Shen YC (2006). Production of valienamine by a newly isolated strain: *Stenotrophomonas maltrophilia*. Enzyme Microb. Technol. 39: 1060-1065.

Zheng YG, Zhang XF, Shen YC (2005b). Microbial transformation of validamycin A to valienamine by immobilized cells. Biocatal. Biotransform. 23: 71-77.