the innate immune system by the virus. Moreover, the expression of TLR3 in T cells and macrophages infiltrating to the pancreas in those patients, is an important evidence of viral infection in fulminant type 1 diabetes. In addition, several TLRs and type I interferon are reported to express simultaneously in immune cells [23], suggesting different types of TLRs might be detectd in a same immunocyte in our specimens. The finding that enterovirus RNA was detected in a beta-cell-positive islet in one of the three patients by *in situ* hybridization is a direct evidence of enterovirus infection in this patient, while Ylipaasto *et al* studied autopsy pancreases from 65 type 1 diabetic patients (not subclassified into type 1A or type 1B) for presence enterovirus RNA by *in situ* hybridization and they found positive results in just 4 out of 65 patients. [24].

Second, both beta and alpha cell regions were decreased significantly in fulminant type 1 diabetes, even very soon after the onset of overt diabetes. The beta cell region in fulminant type 1 diabetes patients was 0.1 % of that in normal controls in our study. We previously reported that the beta cell area was decreased to 0.4 % of that of normal controls in pancreatic biopsy specimens with fulminant type 1 diabetes obtained 1 to 5 months after the onset of overt diabetes. We also reported that the beta cell area in autoimmune (type 1A) diabetes was decreased to only 14.5 % of that in normal controls [8]. These data indicated that almost all the beta cells were destroyed within a short period in fulminant type 1 diabetes. The result contrasts strikingly with type 1A diabetes where the process of beta cell destruction usually progresses gradually [25]. In addition, the alpha cell area in fulminant diabetes was also markedly decreased to 9.6 % of that in normal controls, indicating that both beta and alpha cells are damaged at the onset of fulminant type 1 diabetes. This finding also contrasts to the mild decrease of alpha cells in type 1A diabetes.

Third, we detected the infiltration of CD3+ cells and CD68+ cells in and around the islets, as well as in the exocrine pancreas, in all patients with fulminant type 1 diabetes just after the onset of clinical diabetes. CD68+ macrophages infiltrates predominantly and are observed in 92.6 % of islets examined in this study. In our previous report, no insulitis was observed in the biopsy specimens of three patients obtained 1 to 5 months after onset [2]. Overall, it is reasonable to believe that mononuclear cell infiltration into the islets exist at the time of disease onset but disappear soon after both beta cell destruction and elimination of possible viral antigens in fulminant type 1 diabetes.

From these results, we suggest that not autoimmunity but antiviral inflammation plays an etiopathological role in fulminant type 1 diabetes. In the classical type 1A diabetes, autoimmunity is believed to be an etiology and insulin is the most likely candidate as a primary antigen [25]. It is well known that T cells are dominated in insulitis lesion, alpha cells are not affected, and beta cells are specifically damaged because of selective recognition of beta cell autoantigens by T cells [26]. However, in fulminant type 1 diabetes, the infiltration of macrophages (but not T cells) is dominant. Macrophages are initially activated in viral infected lesion and generate inflammatory cytokines, and chemokines to kill the target cells [27], though it also observed in low-dose Streptozotocin-induced diabetes model mice [28]. They are less selective than T cell-oriented target cell death. This hypothesis of a less selective mechanism is in accord with the fact that both beta and alpha cell regions are decreased significantly in fulminant type 1 diabetes as shown in this study.

In conclusion, our study showed remarkably decreased numbers of pancreatic beta and alpha cells, macrophage-dominated insulitis and the expression of TLRs, a signature of viral infection, in fulminant type 1 diabetes soon after the disease onset. These results suggest a new mechanism of virus-induced macrophage-dominated inflammatory process, rather than autoimmune T cell response, plays a major role in beta cell destruction in this novel subtype of diabetes.

Acknowledgements

We would like to thank Shinobu Mitsui and Fumie Katsube for their excellent technical assistance and Prof. Tadatsugu Taniguchi (University of Tokyo) for the helpful discussion and Dr. Kensuke Miyake (University of Tokyo) for the generous gifts of the antibodies. This study was supported in part by a Grant-in-Aid from the Japanese Society for the Promotion of Science (KAKENHI 19790641, 19591087, 19591069, 21591184), a grant from The Naito Foundation (2007), a grant from Takeda Science Foundation (2007), a Grant-in-Aid from the Japanese Ministry of Health, Labor and Welfare and a grant from Juvenile Diabetes Research Foundation (HH).

References

1. American Diabetes Association (2008) Diagnosis and classification of diabetes mellitus. *Diabetes Care* 31: S55-60.
2. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y for the Osaka IDDM Study Group. (2000) A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. *N Engl J Med* 342: 301-307.
3. Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Toyoda T, Maruyama T, Makino H (2003) Fulminant type 1 diabetes: a nationwide survey in Japan. *Diabetes Care* 26: 2345-2352.
4. Hanafusa T, Imagawa A (2007) Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab* 3: 36-45.
5. Cho YM, Kim JT, Ko KS, Koo BK, Yang SW, Park MH, Lee HK, Park KS (2007) Fulminant type 1 diabetes in Korea: high prevalence among patients with adult-onset type 1 diabetes. *Diabetologia* 50: 2276-2279.
6. Chiou CC, Chung WH, Hung SI, Yang LC, Hong HS (2006) Fulminant type 1 diabetes mellitus caused by drug hypersensitivity syndrome with human herpesvirus 6 infection. *J Am Acad Dermatol* 54: S14-S17.
7. Moreau C, Drui D, Arnault-Ouary G, Charbonnel B, Chaillous L, Cariou B (2008) Fulminant type 1 diabetes in Caucasians: a report of three cases. *Diabetes Metab* 34: 529-532.
8. Sayama K, Imagawa A, Okita K, Uno S, Moriwaki M, Kozawa J, Iwahashi H, Yamagata K, Tamura S, Matsuzawa Y, Hanafusa T, Miyagawa J, Shimomura I (2005) Pancreatic beta and alpha cells are both decreased in patients with fulminant type 1 diabetes: a morphometrical assessment. *Diabetologia* 48: 1560-1564.
9. Tanaka S, Kobayashi T, Momotsu T (2000) A novel subtype of type 1 diabetes mellitus. *N Engl J Med* 342: 1835-1838.
10. Yamazaki M, Hayashi T (2002) Rapid-onset type 1 diabetes mellitus without pancreatic exocrine dysfunction. *Ann Intern Med* 137: 145-146.
11. Imagawa A, Hanafusa T, Uchigata Y, kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Maruyama T, Makino H (2005) Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. *Diabetologia* 48: 294-300. *Erratum in: Diabetologia* (2008) 51: 524-526.
12. Kawasaki E, Imagawa A, Makino H, Uga M, Abiru N, Hanafusa T, Uchigata Y, Eguchi K (2008) Differences in the contribution of CTLA4 gene to susceptibility to fulminant and type 1A diabetes in Japanese patients. *Diabetes Care* 31: 1608-1610.
13. Imagawa A. Hanafusa T, Makino H, Miyagawa J, Juto P (2005) High titres of IgA antibodies to enterovirus in fulminant type-1 diabetes. *Diabetologia* 48: 290-293.
14. Sano H, Terasaki J, Tsutsumi C, Imagawa A, Hanafusa T (2008) A case of fulminant type 1 diabetes mellitus after influenza B infection. *Diabetes Res Clin Pract* 79: e8-9.
15. Goto A, Takahashi Y, Kishimoto M, Nakajima Y, Nakanishi K, Kajio H, Noda M (2008) A case of fulminant type 1 diabetes associated with significant elevation of mumps titers. *Endocr J* 55: 561-564.
16. Hanafusa T, Imagawa A, Iwahashi H, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Maruyama T, Makino H (2008) Report of the Japan Diabetes Society's committee on research on fulminant type 1 diabetes mellitus: Analysis of antiviral antibodies at disease onset. *J Japan Diab Soc* 51 :531-536.
17. Itoh N, Hanafusa T, Miyazaki A, Miyagawa J, Yamagata K, Yamamoto K, Waguri M, Imagawa A, Tamura S, Inada M, Kawata S, Tarui S, Kono N, Matsuzawa Y (1993) Mononuclear cell infiltration and its relation to the expression of major histocompatibility complex antigens and adhesion molecules in pancreas biopsy specimens from newly diagnosed insulin-dependent diabetes mellitus patients. *J Clin Invest* 92: 2313-2322.
18. Oikarinen M, Tauriainen S, Honkanen T, Oikarinen S, Vuori K, Kaukinen K, Rantala I, Mäki M, Hyöty H (2008) Detection of enteroviruses in the intestine of type 1 diabetic patients. *Clin Exp Immunol* 151: 71-75.
19. Oikarinen M, Tauriainen S, Honkanen T, Vuori K, Karhunen P, Vasama-Nolvi C, Oikarinen S, Verbeke C, Blair GE, Rantala I, Ilonen J, Simell O, Knip M, Hyöty H (2008) Analysis of pancreas tissue in a child positive for islet cell antibodies. *Diabetologia* 51: 1796-1802.
20. Hohenadl, C, Klingel, K, Mertsching, J, Hofschneider PH, Kandolf R (1991) Strand-specific detection of enteroviral RNA in myocardial tissue by in situ hybridization. *Mol Cell Probes* 5: 11-20.
21. Ylipaasto P, Kutlu B, Rasilainen S, Passchaert J, Salmera K, Teerijoki H, Korsgren O, Lahesmaa R, Hovi T, Eizirik DL, Otonkoski T, Roivainen M (2005) Global profiling of coxsackievirus- and cytokine-induced gene expression in human pancreatic islets *Diabetologia* 48: 1510-1522.
22. Hultcrantz M, Hühn MH, Wolf M, Olsson A, Jacobson S, Williams BR, Korsgren O, Flodström-Tullberg M (2007) Interferons induce an antiviral state in human pancreatic islet cells. *Virology* 367: 92-101.
23. Komatsuda A, Wakui H, Iwamoto K, Ozawa M,

Togashi M, Masai R, Maki N, Hatakeyama T, Sawada K (2008) Up-regulated expression of Toll-like receptors mRNAs in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Clin Exp Immunol* 152: 482-487.

24. Ylipaasto P, Klingel K, Lindberg AM, Otonkoski T, Kandolf R, Hovi T, Roivainen M (2004) Enterovirus infection in human pancreatic islet cells, islet tropism in vivo and receptor involvement in cultured islet beta cells. *Diabetologia* 47: 225-239
25. Eisenbarth GS (2007) Update in type 1 diabetes. *J Clin Endocrinol Metab* 92: 2403-2407.
26. Moriwaki M, Itoh N, Miyagawa J, Yamamoto K, Imagawa A, Yamagata K, Iwahashi H, Nakajima H, Namba M, Nagata S, Hanafusa T, Matsuzawa Y (1999) Fas and Fas ligand expression in inflamed islets in pancreas sections of patients with recent-onset Type I diabetes mellitus. *Diabetologia* 42: 1332-40.
27. Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. *Cell* 124: 783-801.
28. Ihm SH, Lee KU, Rhee BD, Min HK (1990) Initial role of macrophage in the development of anti-beta cell cellular autoimmunity in multiple low-dose streptozotocin-induced diabetes in mice. *Diabetes Res Clin Pract* 10: 123-126.

[3] Kiilavuori K, Sovijarvi A, Naveri H, Ikonen T, Leinonen H. Effect of physical training on exercise capacity and gas exchange in patients with chronic heart failure. Chest 1996;110:985–91.
[4] Oka RK, De Marco T, Haskell WL, et al. Impact of a home-based walking and resistance training program on quality of life in patients with heart failure. Am J Cardiol 2000;85:365–9.
[5] Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:117–82.
[6] DiPietro L, Caspersen C, Ostfeld A, Nadel E. A survey for assessing physical activity among older adults. Med Sci Sports Exerc 1993;25:628–42.
[7] Guyatt G, Nogradi S, Halcrow S, Singer J, Sullivan M, Fallen E. Development and testing of a new measure of health status for clinical trials in heart failure. J Gen Med 1989;4:101–7.
[8] Heiat AG, Cary P, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002;162:1682–8.
[9] Bennett JA, Riegel B, Bittner V, Nichols J. Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. Heart Lung 2002;31:262–70.
[10] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.

0167-5273/$ – see front matter
doi:10.1016/j.ijcard.2009.09.478

Connexin 43 expression is associated with vascular activation in human radial artery

Kumiko Arishiro [a,1], Masaaki Hoshiga [a,*], Tadashi Ishihara [a], Keiichiro Kondo [b], Toshiaki Hanafusa [a]

[a] First Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan
[b] Department of Thoracic Surgery, Osaka Medical College, Takatsuki, Japan

ARTICLE INFO

Article history:
Received 7 September 2009
Accepted 10 September 2009
Available online 27 October 2009

Keywords:
Atherosclerosis
Gap junction
Nuclear factor kappa B

The gap junction protein, connexin 43 (Cx43), might be involved in the development of atherosclerosis. Cx43 is expressed in vascular smooth muscle cells (SMCs) and its upregulation has been reported in animal models with atherosclerosis [1]. However, little is known about Cx43 expression in human arteries [2]. Here, we examined Cx43 expression in radial arteries (RA) and internal thoracic artery (ITA) of patients undergoing coronary artery bypass graft (CABG) surgery.

Short lengths of both the distal RA and ITA were obtained from 29 Japanese patients at the time of CABG surgery. Table 1 shows the patient characteristics. Frozen sections of both arteries were analyzed immunohistochemically using anti-human Cx43 (Chemicon) and anti-activated nuclear factor kappa B (NFκB) (p65 subunit) (Cell Signaling Technology) antibodies. Elastic fibers were stained with elastica van Gieson (eVG).

Staining the RA with eVG revealed homogeneously muscular types with little elastic laminae. The intensity of Cx43 in the medial SMC differed among individual patients. Activated NFκB often colocalized with Cx43 expression (Fig. 1). The intensity of Cx43 expression positively correlated with NFκB activation ($r=0.74$, $P<0.01$; Fig. 1E).

In contrast, eVG staining revealed a heterogeneous ITA structure, ranging from elastic to muscular artery. The expression of Cx43 was prominent in the elastic ITA type, whereas its expression was sparse in the muscular type. The number of elastic laminae significantly and positively correlated with Cx43 expression ($r=0.61$, $P<0.01$). The expression of Cx43 did not correlate with NFκB activation in ITA at all. Moreover, the intensity of Cx43 expression in ITA did not correlate with that in RA of any patient.

We found Cx43 expression was associated with NFκB activation in the human RA, which is a muscular artery. As NFκB activation is a key signal for the induction of various proinflammatory cytokines, Cx43 upregulation seems to be involved in the pathogenesis of atherosclerosis in the human muscular artery. Interestingly, Cx43 expression differed between RA and ITA even within the same patient. Cx43 expression in ITA of Japanese individuals depended on the number of elastic fibers as found in Caucasians [3]. Previous histological study suggested that ITA with more elastic media possesses less intima [4]. Various studies in animal models suggest that the upregulation of Cx43 expression in SMC is linked to the development of

Table 1
Patient characteristics.

	All subjects ($n=29$)
Age, years	62±9
Gender (male, %)	25 (86.2)
SBP, mm Hg	128±19
DBP, mm Hg	77±11
Risk factor	
Smoking, %	18(62.1)
DM, %	16(55.2)
Hyperlipidemia, %	18(62.1)
Hypertension, %	19(65.5)
CRP (mg/dl)	0.119±0.105
Previous cardiovascular events (OMI/AP)	4/25

Values are mean±SD or number and percentage of patients.
SBP, systoric blood pressure; DBP, diastolic blood pressure.
CRP, C-reactive protein.

* Corresponding author. First Department of Internal Medicine, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan.
E-mail address: in1026@poh.osaka-med.ac.jp (M. Hoshiga).
[1] Present address: Department of Internal Medicine, Osaka Dental University, Osaka, Japan.

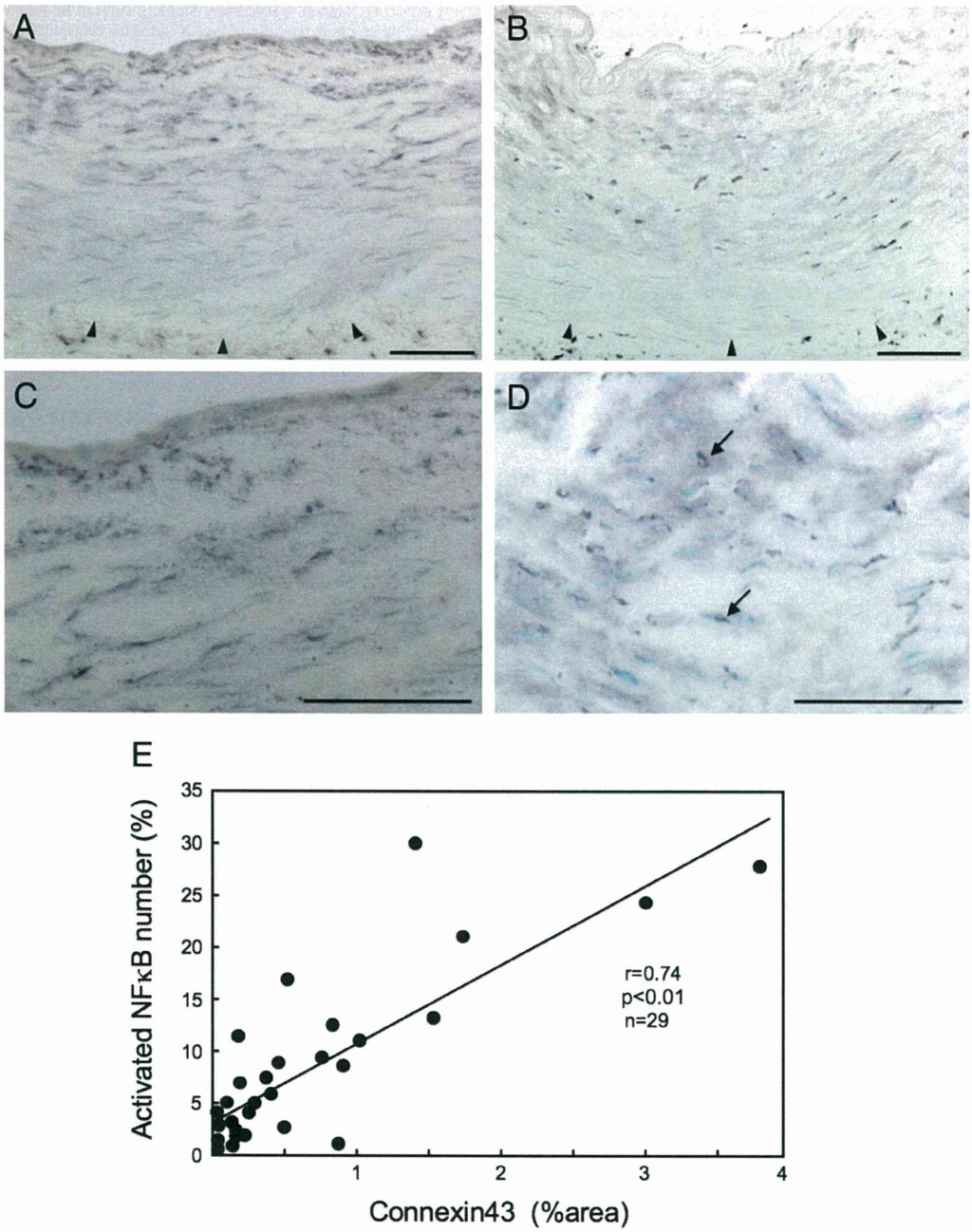

Fig. 1. Connexin 43 expression and NFκB activation in RA. Immunohistochemical staining for connexin 43 (A and C) and NFκB p65 subunit (B and D) in media of RA. C and D, positive staining at greater magnification. Arrowheads, external elastic laminae. Arrows, positive staining for NFκB p65 subunit. Bar, 100 μm. E, positive relationship between intensity of connexin 43 and NFκB p65 expression. RA, radial artery. NFκB, nuclear factor kappa B.

atherosclerosis [1,5]. Thus the regulation of Cx43 expression on medial SMC in ITA seems unique, whereas that in RA is universal. In addition, RA and coronary artery are similar in that they are both of the muscular type. Thus, Cx43 expression might be involved in the development of coronary atherosclerosis.

The fact that increased Cx43 expression correlated with NFκB activation in the distal portion of RA is of interest because bypasses might fail in patients with an RA bypass conduit in that location. In fact, bypasses became occluded at the RA-coronary anastomosis sites within 2 years of CABG in two of our patients who expressed high levels of Cx43 and activated NFκB in RA sections. Although we could not follow the remote patency of bypass conduits in all of the patients, Cx43 expression might be involved in its remote patency. Thus a strategy to decrease Cx43 expression in RA conduits might be useful in the clinical setting.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

References

[1] Yeh HI, Lupu F, Dupont E, Severs NJ. Upregulation of connexin43 gap junctions between smooth muscle cells after balloon catheter injury in the rat carotid artery. Arterioscler Thromb Vasc Biol 1997;17:3174–84.

[2] Blackburn JP, Peters NS, Yeh HI, Rothery S, Green CR, Severs NJ. Upregulation of connexin43 gap junctions during early stages of human coronary atherosclerosis. Arterioscler Thromb Vasc Biol 1995;15:1219–28.
[3] Ko YS, Yeh HI, Haw M, et al. Differential expression of connexin43 and desmin defines two subpopulations of medial smooth muscle cells in the human internal mammary artery. Arterioscler Thromb Vasc Biol 1999;19:1669–80.
[4] van Son JA, Smedts F, de Wilde PC, et al. Histological study of the internal mammary artery with emphasis on its suitability as a coronary artery bypass graft. Ann Thorac Surg 1993;55:106–13.
[5] Chadjichristos CE, Matter CM, Roth I, et al. Reduced connexin43 expression limits neointima formation after balloon distension injury in hypercholesterolemic mice. Circulation 2006;113:2835–43.
[6] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.

0167-5273/$ – see front matter
doi:10.1016/j.ijcard.2009.09.479

The stoichiometric relationship between KCNH-2 and KCNE-2 in I_{Kr} channel formation☆

Do-Geun Kim [a], Jung-Hwa Oh [a], Eun-Hee Lee [a,b], Jong-Hwa Lee [a], Han-Jin Park [a], Choong-Yong Kim [a], Myung-Sang Kwon [a,c], Seokjoo Yoon [a,b,*]

[a] Korea Institute of Toxicology, 100 Jangdong, Yuseong, Daejeon, 305-343, Republic of Korea
[b] Pharmacology and Toxicology, School of Engineering, University of Science and Technology, 113 Gwahangno, Yuseong, Daejeon, 305-333, Republic of Korea
[c] School of Veterinary Medicine, Kangwon National University, Chunchon, Republic of Korea

ARTICLE INFO

Article history:
Received 23 June 2009
Revised 25 August 2009
Accepted 9 September 2009
Available online 13 November 2009

Keywords:
KCNH-2
KCNE-2
Stoichiometric relationship
Real-time PCR
Western blotting

Ventricular arrhythmias are caused by reentrant circuits that occur due to the blockade of a conduction circuit in the muscle of the heart [1]. Torsade des pointes (TdP), a type of ventricular tachycardia characterized by twisting of the wave on an electrocardiogram, may be caused by the malfunctioning of inwardly rectifying potassium channels (I_{Kr} channels), which play significant roles in phase 3 of the cardiac action potential [2].

The pores of I_{Kr} channels are encoded by two genes, *KCNH-2* and *KCNE-2*, which serve as alpha- and beta-subunits, respectively. Mutations in either of these genes can cause long QT-like syndromes [3–6].

However, contrary to the assumption that the expression of KCNE-2 exceeds that of KCNH-2, a number of articles have shown that the ratio of *KCNH-2* mRNA to *KCNE-2* mRNA is inadequate to support the formation of a channel complex (i.e., the expression of KCNH-2 is much higher than that of KCNE-2) and this has resultantly lead to the weakness of KCNH-2 and KCNE-2 complex theory [7–9].

In this study, we examined the stoichiometric relationship between *KCNE-2* and *KCNH-2* to confirm whether the proteins they encode comprise a functional channel in cardiac muscle. To do so, we evaluated the expression of the two genes at the mRNA level by real-time polymerase chain reaction (PCR) and microarray analysis and at the protein level by Western blotting. The stoichiometry between two proteins was obtained using densitometer.

mRNA was extracted from the ventricles of 6-week-old SD rats ($n=3$; Orient Bio, Seongnam, Korea) using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions and purified using an RNeasy Total RNA Isolation Kit (Qiagen, Hilden, Germany). Total RNA from the hearts of three individuals was quantified using a NanoDrop ND-1000 spectrophotometer (Wilmington, DE) and its integrity was assessed using a 2100 Bioanalyzer (Agilent, Böblingen, Germany). *KCNE-2* and *KCNH-2* mRNA were detected and quantified using SYBR Green (QunatiTect SYBR Green PCR Master Mix; Qiagen, Valencia, CA) according to the manufacturer's instructions using a Rotor Gene 6000 real-time rotary analyzer (Corbett Research, Sydney, Australia). Primers were designed using Primer 3 software (http://frodo.wi.mit.edu/; Table 1 in Appendix A). To ensure the specificity and integrity of the amplified products, melting curve analyses were performed on all amplified products. *GAPDH* was used as an internal control, and the fold-changes in expression were calculated according to the $2^{-\Delta\Delta CT}$ method. For the microarray analysis, an Affymetrix Rat Genome 230 2.0 array was used; all processing was performed according to the manufacturer's instructions (Affymetrix, Santa Clara, CA). Data processing of the cell intensity files (CEL) and microarray analysis were performed using GenPlex software (Istech Inc., Goyang, Korea). The data were normalized by global-scale normalization. The accession numbers of each probe used in the detection of *KCNH-2* and *KCNE-2* are given in Table 2 in Appendix A.

Astemizole (60 mg/kg), a selective I_{Kr} blocker, was administered to 6-week-old SD rats ($n=3$; Orient Bio) by oral gavage; rats given an equal volume of 0.5% methylcellulose ($n=3$) were included as a control. Four hours later, the rats' hearts were collected under isoflurane and RNA was extracted for microarray analysis as described above. Changes in the mRNA expression of *KCNH-2* and *KCNE-2* in response to astemizole were subsequently determined.

For deglycosylation study of KCNE-2, approximately 50 mg ventricular muscle was isolated from the 6-week-old SD rats ($n=3$). The samples were lysed with lysis buffer and automated sonicator. 60 μg of lysed samples was incubated with N-glycosidase at 37 °C for

☆ The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, see: http://www.textcheck.com/certificate/xRKStB.

* Corresponding author. Korea Institute of Toxicology, 100 Jangdong, Yuseong, Daejeon, 305-343, Republic of Korea. Tel.: +82 42 860 7476; fax: +82 42 860 7488.
E-mail address: sjyoon@kitox.re.kr (S. Yoon).