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Expression of tyrosine hydroxylase and growth-associated protein 43 in aging patients with atrial fibrillation of Xinjiang Uygur and Han nationalities

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This study explores the changes in gene and protein expression of tyrosine hydroxylase (TH) and growth-associated protein 43 (GAP43) in aging patients with atrial fibrillation of Xinjiang Uygur and Han nationalities. Real-time polymerase chain reaction (PCR) and Western blot were used to detect the gene and protein expressions of TH and GAP43 in atrial tissues of 54 patients with valvular heart disease. Comparison of the mRNA and the protein expression of GAP43 and TH between the sinus rhythm group and the atrial fibrillation group was statistically significant ($P < 0.05$); the protein expression of GAP43 and TH in patients of Xinjiang Uygur and Han nationalities in the sinus rhythm group and atrial fibrillation group was statistically significant ($P < 0.05$); the protein expression of GAP43 and TH in patients of different nationalities in the sinus rhythm group and atrial fibrillation group was not statistically significant ($P > 0.05$); the protein expression of GAP43 and TH in patients of different nationalities with different ages in the sinus rhythm group and atrial fibrillation group was not statistically significant ($P < 0.05$); only the protein expression of GAP43 in patients with different ages in the atrial fibrillation group was statistically significant ($P < 0.05$). The changes in mRNA and protein expression of TH and GAP43 played a vital role in the process of maintaining atrial fibrillation. The increase in the expression of TH and GAP43 may be one of the molecular bases of the left atrial myoelectricity remodeling of aging patients with atrial fibrillation. TH and GAP43 may be the potential therapeutic targets of atrial fibrillation.

Key words: Atrial fibrillation (AF), aging, Xinjiang Uygur, Han nationality, tyrosine hydroxylase (TH), growth associated protein (GAP43)

INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmia in clinical cardiac diseases, the morbidity of which is closely related with the age of the patients. AF may attack anyone, but it has high morbidity in aged individuals and extremely low morbidity in children. The morbidity rate of AF is above 0.4% among common people. The morbidity rate rises significantly with increasing age, which reaches 6% for those who are above 65, 10% for those who are above 75, and even near 20% for those who are above 85 (Nattel et

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al., 2008). The continuous existence of AF easily causes serious complications such as heart failure, intra-atrial thrombus, cerebral embolism, etc., which have a high disability and mortality rates (Fuster et al., 2001; Tsang et al., 2005). Currently, many therapeutic methods are available for the treatment of AF, including drug therapy, electrical conversion, surgical maze operation treatment, radiofrequency catheter ablation, pacemaker implantation, etc. However, given that none of them is completely satisfactory, a study on the mechanism of occurrence and maintenance of AF is necessary.

In recent years, the function of neural regeneration in AF myoelectricity remodeling has gained increasing attention. Many studies found that the function change in the cardiac autonomic nerve plays an important role in inducing AF (Wijffels et al., 1995; Chen and Tan, 2007). Tyrosine hydroxylase (TH) and growth associated protein 43 (GAP43) are important factors in the regeneration and distribution of cardiac autonomic nerves. In a previous study (Horikawa-Tanami et al., 2007), TH was found to be a sign factor of the sympathetic nerve and GAP43 was found to be a sign factor of the parasympathetic nerve; TH and GAP43 could play an important role in the process of AF formation, maintenance, and recovery.

Xinjiang is located in Northwest China, where the economy is relatively backward. Most people have minority nationalities, mainly the Uyghur nationality. Given these minorities' unique customs and religious beliefs, intermarriage is discouraged between the people of Uygur nationality and other nationalities, making the genes of Uygur nationality relatively pure. Epidemiological studies found that the prevalence of AF among Uygur people is higher than that among people of other nationalities in this region. In this study, changes in TH and GAP43 expressions in patients of Uygur and Han nationalities in Xinjiang region were detected. The study aimed to find the genetic differences between the two nationalities and provide a new theoretical basis for better AF treatment.

MATERIALS AND METHODS

Patients

The study subjects were 54 patients from in the First Affiliated Hospital of Xinjiang Medical University who suffered from valvular heart disease and needed open chest valve replacement operation from 2008 to 2011. Among the 54 cases, 28 were of Han nationality and 26 were of Uygur nationality, and 22 were male and 32 were female. Their ages ranged from 43 to 72 (46.28 ± 9.15). The 54 patients were divided into two groups: sinus rhythm group and AF group. Of the 26 cases in the sinus rhythm group, 14 were male patients and 12 were female patients, with an average age of 53.38 ± 12.74. Of the 28 cases in the AF group, 8 were male patients and 20 were female patients, with an average age of 55.29 ± 8.58. Eight cases of paroxysmal AF and 18 cases of chronic AF (AF lasting more than 6 months) were included in the AF group. All patients used cordarone (oral administration or intravenous injection) to control their ventricular rate. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. Written informed consent was obtained from all participants.

Inclusion criteria and exclusion criteria

Before valvular surgery, AF and sinus rhythm were confirmed by clinical query and dynamic electrocardiogram (ECG). The telemetry ECG was used to record and review the status of patients within 7 days after admission. AF with duration longer than 7 days and shorter than 48 h was defined as persistent AF and paroxysmal AF, respectively. In the sinus rhythm group, patients with atrial arrhythmia and heart palpitations were excluded. Coronary arteriography was performed on partial patients to exclude the possibility of coronary heart disease. All patients had no liver or kidney function damage, electrolyte disturbance, infection, hypertension, hyperthyroidism, or diabetes mellitus. Their heart functions were at grade II to III (NYHA grading).

Specimen collection and preservation

The clinical baseline data of the patients were registered, and informed consent forms were signed before the operation. Extracorporeal circulation was established during the operation, and approximately 200 mg of left auricle tissues was taken out after cardiac arrest. The left auricle tissues were immediately put into liquid nitrogen after blood and fat tissues were excluded, followed by preservation in a -80°C low-temperature refrigerator for further usage.

Real-time polymerase chain reaction (PCR)

Left auricle tissues with a weight of 100 mg were taken, and the total RNA was extracted through the Trizol one-step method (Invitrogen Company). Total RNA of 1 µg was taken and reverse transcriptased into cDNA according to the instruction of the Reverse Transcription Kit (Promega Company A3500).

Design and synthesis of the primer: primer was synthesized by TaKaRa Company (Table 1). Real-time PCR system (20 µl): specimens for detection were given cDNA 2-fold dilution. About 1 µl cDNA was taken using 10 µl SybrGreen qPCR Master Mix (Shanghai Ruian BioTechnologies), 1 µl upstream primer (10 µM), 1 µl downstream primer (10µM), and 7 µl ddH_2o. Reaction conditions: reaction conditions were 10 min at 95°C initial denaturation, followed by PCR circulation, 15 s at 95°C denaturation, 30 s annealing at 60°C, 20 s at 72°C extension, and 40 circulations. Reflected light signals were collected. $2^{-\Delta\Delta}$Ct method was used to calculate the relative mRNA expression value of the target gene.

Western blotting

The total protein of the tissues was extracted according to the kit instruction (Beijing Solarbio). The content of the total protein was detected using the bicinchoninic acid (BCA) method. The total protein was separated through electrophoresis using polyacrylamide gel (SDS-PAGE). The sample loading of each hole was 50 µg. The protein in the gel was then blotted to nitrocellulose (NC) film through galvanic transferring. After sealing and elution using 5% nonfat dry milk/Tris-buffered saline (TBS) solution, hybridization was carried out by TH-specific first resistance (Anti-rabbit IgG, Abcam Company), GAP43-specific first resistance (Anti-rabbit IgG, Abcam Company), and β-actin channel protein-specific first resistance (Anti-rabbit IgG, Wuhan Boster Company), respectively, followed by 4°C overnight incubation. Incubation for 1 h followed using specific second resistance (Goat Anti-rabbit IgG, Wuhan

Table 1. Design and synthesis of the primer.

Gene	Primer sequence	Amplified fragment length (bp)
β-actin	F:GCTACGAGCTGCCTGACG; R:TCGTGGATGCCACAGGAC	112
TH	F:TGTTCCAGTGCACCCAGTATATC; R:5'-CCAATGTCCTGCGAGAACTG	136
GAP43	F:AGAACATAGAAGCTGTAGATGAAAC; R:CCATTTCTTAGAGTTCAGGCAT	112

Boster Company) indicated by horseradish peroxidase. Diaminobenzidine (DAB) coloring was carried out. All hybridization signals were scanned quantitatively by the BIO-RAD gel imaging system.

Statistical analysis

EXCEL 2003 software was used for data collection. Statistical analysis software (SAS) JMP package was used for the statistical analysis. Mean ± standard deviation ($\bar{x} \pm s$) was used for the general description of age. Left atrial (LA), right atrium (RA), and ejection fractions (EF) were used for the sinus rhythm and AF groups. Constituent ratio and constituent rate were used for the gender and nationality constituents. T- or t`-test was used for comparing the general data in the sinus rhythm and AF groups under the premise of conducting a homogeneity test for variance. T-test was used for comparing the GAP43 and TH difference between the sinus rhythm group and the AF group, with nationality and age used as the covariant. T-test was also used for comparing the GAP43 and TH difference in the different nationalities and ages, with disease used as the covariant. The inspection level used was 0.05.

RESULTS

General information

The left atrial diameter of patients in the AF group exceeded that of the patients in the sinus rhythm group. No statistical significance was observed in the other clinical data of the two groups, such as, age, nationality, gender, ejection fraction, cardiac functional grading (NYHA Grading), etc (Table 2).

mRNA and protein expression

The mRNA and protein expressions of GAP43 and TH in the sinus rhythm group and the AF group were compared. The results showed a statistical significance ($P < 0.05$) in the mRNA and protein expressions of TH and GAP43 (Table 3).

GAP43 and TH protein expression

The difference in protein expression of GAP43 and TH between the sinus rhythm and AF groups was compared, with Han and Uygur nationalities used as the covariant. The results showed a statistical significance in the GAP43 and TH protein expression of the Xinjiang Uygur and Han nationalities between the sinus rhythm and AF groups ($P < 0.05$) (Table 4).

Different nationalities

The difference in the GAP43 and TH protein expression between the two nationalities was compared, with different diseases used as the covariant. No statistical significance was observed in the GAP43 and TH protein expressions of the two nationalities between the sinus rhythm and AF groups ($P > 0.05$) (Table 5).

Different ages

The difference in protein expressions of GAP43 and TH between the sinus rhythm and AF groups was compared, with different nationalities used as the stratification factors. The results showed a statistical significance in the difference between the sinus rhythm and AF groups ($P < 0.05$) (Table 6).

The difference in the GAP43 and TH protein expressions in different ages between the sinus rhythm and AF groups was compared, with diseases used as the stratification factors. The results showed that only the protein expression of GAP43 in different ages in the AF group was statistically significant ($P < 0.05$) (Table 7).

DISCUSSION

Earlier studies indicated that stimulating the vagus nerve and acetylcholine administration could cause significant cardiac electrophysiological changes; the former could cause the shortening of the atrial refractory period, which will induce AF (Brundel et al., 2004). High-frequency electrical stimulation on the cardiac ganglionated plexi (GP) might trigger activity originating from the pulmonary veins, which could induce AF (Hauerte et al., 2001). On the basis of atrial premature stimulation, stimulating epicardial fat (which contains GP) could also lead to AF (Scherlag et al., 2005). Radiofrequency ablation of GP could reverse the changes in the atrial refractory period and eliminate the capacity of premature stimulation, which influences the superior pulmonary vein and induces

Table 2. Comparison of clinical features between two groups ($\bar{x} \pm s$).

Parameter	Sinus rhythm group (n = 26)	AF group (n = 28)	Statistic	P
Nationality, n (%)				
Han	10 (36)	18 (64)	χ^2 = 3.60	0.058
Uygur	16 (62)	10 (38)		
Gender, n (%)				
Male	14 (64)	8 (36)	χ^2 = 3.567	0.059
Female	12 (10)	20 (90)		
Age (years)	53.38 ± 12.74	55.29 ± 8.58	t′=-0.641	>0.05
LA (mm)	45.09 ± 7.73	57.90 ± 11.36	t= 4.807	0.000
RA (mm)	42.94 ± 8.47	45.37 ± 19.12	t′=0.611	>0.05
EF (%)	63.33 ± 11.15	61.31 ± 6.60	t′=0.802	>0.05

After test for homogeneity of variance, t` test was used for age, RA and EF comparison due to heterogeneity of variance (F_{age} = 2.2048, P_{age} = 0.0472; F_{RA} = 5.0958, P_{RA} = 0.0001, F_{EF} = 2.8541, P_{EF} = 0.0090). Homogeneity of variance was reported in LA between two groups. LA = Let atrium; RA = right atrium; EF = ejection fraction.

Table 3. The mRNA and protein expression of GAP43 and TH in two groups ($\bar{x} \pm s$).

Parameter	GAP43		TH	
	mRNA	Protein	mRNA	Protein
Sinus rhythm group (n = 26)	0.86 ± 0.23	0.28 ± 0.21	0.06 ± 0.03	0.64 ± 0.30
AF group (n = 28)	2.19 ± 0.73	0.85 ± 0.38	0.13 ± 0.05	1.03 ± 0.42
Statistic	9.163*	6.885*	6.289*	3.900*
P	<0.05	<0.05	<0.05	0.000

*Heterogeneity of variance: t` test.

Table 4. The difference of protein expression of GAP43 and TH in two groups ($\bar{x} \pm s$).

Nationality	Parameter	GAP43	TH
Han	Sinus rhythm group (n = 10)	0.26 ± 0.01	0.36 ± 0.11
	AF group (n = 18)	0.76 ± 0.35	0.87 ± 0.52
	Statistic	5.956*	4.003*
	P	0.000	<0.05
Uygur	Sinus rhythm group (n = 16)	0.29 ± 0.27	0.42 ± 0.19
	AF group (n = 10)	1.02 ± 0.40	1.05 ± 0.40
	Statistic	5.5737#	4.663*
	P	0.000	<0.05

*Heterogeneity of variance: t` test; #Homogeneity of variance: t test.

induces AF (Nakagawa et al., 2004). Further studies (Patterson et al., 2005) confirmed that the rapid discharge of the vein is the combined action result of the sympathetic and parasympathetic neurotransmitters. Many studies showed that the functional changes in the autonomic nerves could induce AF. The study of Wijffels et al. (1995) confirmed that stimulating the vagus nerve could cause the shortening of the atrial muscle cell

Table 5. The difference of protein expression of GAP43 and TH in different nationalities in two groups ($\bar{x} \pm s$).

Group	Nationality	GAP43	TH
Sinus rhythm group	Han (n = 10)	0.26 ± 0.01	0.36 ± 0.11
	Uygur (n = 16)	0.29 ± 0.27	0.42 ± 0.19
	Statistic	0.444#	1.019*
	P	>0.05	>0.05
AF group	Han (n = 18)	0.76 ± 0.35	0.87 ± 0.52
	Uygur (n = 10)	1.02 ± 0.40	1.05 ± 0.40
	Statistic	1.791#	0.947#
	P	0.085	0.352

*Heterogeneity of variance: t` test; #Homogeneity of variance: t test.

Table 6. The difference of protein expression of GAP43 and TH in different ages in two groups ($\bar{x} \pm s$).

Age	Parameter	GAP43	TH
≤65	Sinus rhythm group (n = 22)	0.23 ± 0.46	0.51 ± 0.23
	AF group (n = 14)	0.60 ± 0.24	0.76 ± 0.21
	Statistic	5.756*	3.286#
	P	0.000	0.002
>65	Sinus rhythm group (n = 4)	0.53 ± 0.50	0.49 ± 0.28
	AF group (n = 14)	1.10 ± 0.34	1.18 ± 0.58
	Statistic	2.679#	2.268#
	P	0.017	0.038

*Heterogeneity of variance: t` test; #Homogeneity of variance: t-test.

Table 7. The difference of protein expression of GAP43 and TH in two groups in different ages ($\bar{x} \pm s$).

Group	Age	GAP43	TH
Sinus rhythm group (n=26)	≤65 years (n=22)	0.23 ± 0.46	0.51 ± 0.23
	>65 years (n=4)	0.53 ± 0.50	0.49 ± 0.28
	Statistic	1.186#	0.155#
	P	0.247	0.878
AF group (n=28)	≤65 years (n=14)	0.60 ± 0.24	0.76 ± 0.21
	>65 years (n=14)	1.10 ± 0.34	1.18 ± 0.58
	Statistic	4.495#	2.548*
	P	0.000	<0.05

*Heterogeneity of variance: t` test; #Homogeneity of variance: t test.

effective refractory period, which would induce AF. Recent studies also found that the pulmonary vein could induce AF, because of the existence of special cells with electric conduction function in the pulmonary vein. The

cells contain rich sympathetic cells, the activity of which can cause local depolarization, which induces AF (Chen and Tan, 2007). The autonomic nerve abnormal activity can also induce AF by inducing cardiac intracellular calcium overload and early after depolarization (EAD). In their studies, Burashnikov and Antzelevitch (2003) found that injecting acetylcholine into the coronary artery could shorten the action potential of the atrial muscle cell and cause rapid atrial pacemaking, which would easily induce AF. They also found that the sudden stop of AF or the increased rapid pacemaking frequency could instantly improve the tension of the atrial muscle cell, which would cause the three phases of rapid EAD of action potential and extrasystole, thus inducing AF. In their studies, Patterson et al. (2006) found that the continuous increase in relaxing period tension is an important cause of EAD. The increased intracellular calcium concentration in the relaxing period induces AF. By using optical mapping technique, Chou et al. (2005) detected that, when the atrial muscle cell membrane and pulmonary vein regeneration or the nerve automatic activity of dogs decreases the forming rate of cardiac intracellular calcium overload and EAD decreases significantly, which will promote the recovery of AF.

Current studies showed that the mechanism of AF is very complex. The autonomic nervous system (ANS) plays a vital role in triggering and maintaining AF. At present, TH and GAP43 are the main markers related to the regeneration and distribution of the cardiac autonomic nerve. TH is a rate-limiting enzyme that catalyzes the synthesis of the catecholamine neurotransmitter. TH is expressed abundantly in the sympathetic ganglia and noradrenergic neuron of the sympathetic nerve. The positive expression of TH represents the sympathetic nerve distribution in the heart. GAP43 is a fast transport cell membrane phosphate expressed in the sprouting axon growth hillock. GAP43 is distributed extensively in the ANS neurons and is closely related to neural development, regeneration of axons, and reconstruction of synapsis and neurotransmitter release. In summary, GAP43 is regarded as an inherent determinant of neuron development and regeneration. It symbolizes neural development, and it can be used to evaluate ANS growth activity.

Recent studies have expanded the further understanding of the relationship between ANS and AF. In 2001, Chang et al. (2001) established the chronic AF model by rapid atrial pacing. Immunohistochemical method was used to detect the atrium cordis, auricular appendix, eruption of atrial septum nerve, and distribution of the sympathetic nerve in dogs. They found a significant and inhomogeneous neural eruption and the over-distribution of the sympathetic nerve in the atrium cordis of dogs. The right atrium significantly exceeded the left one. Based on former studies, they proposed that the reconstruction of neural tissues could play a vital role in the triggering and maintenance of AF. Gould et al. (2006) provided histological evidence for the reconstruction of the atrial sympathetic nerve in persistent AF patients by comparing the sinus rate and the eruption and distribution levels of the sympathetic nerve in auricular appendix tissues, further confirming that the reconstruction of the autonomic nerve partially triggers AF.

In 2009, Furukwa et al. (2009) made atrioventricular block dog models by applying the radiofrequency ablation method. Atrial enlargement, myocardial fibrosis, and atrial and pulmonary vein (PV) effective refractory period shortening significantly occurred when the sympathetic nerve was stimulated. Atrial conduction velocity accelerated eight weeks later, which did not appear when the vagus nerve was stimulated. In the radiofrequency ablation group, the triggering rate of persistent AF increased upon sympathetic nerve stimulation during sham operation. The triggering rate of persistent AF increased when the vagus nerve was stimulated. Studies indicated that the sympathetic nerve stimulation was a key factor in AF triggering in the reconstructed atria, which is different from the normal atria. The internal diameter enlargement of the left atria is regarded as an important factor in triggering and maintaining AF. Patients in the AF group had a significantly larger left atria than patients in the sinus rhythm group, which had statistical significance ($P < 0.05$). The mRNA and protein expressions of GAP43 and TH in the sinus rhythm and AF groups were compared. The results showed that the mRNA and protein expressions of TH and GAP43 were statistically significant ($P < 0.05$), which indicates that the reconstruction of neural tissues was combined with the structure reconstruction in AF patients.

The difference of protein expression of GAP43 and TH in the sinus rhythm and AF groups was also compared. The results showed a statistical significance in the protein expressions of GAP43 and TH in patients of Xinjiang Uygur and Han nationalities in the sinus rhythm and AF groups ($P < 0.05$). The difference in protein expression of GAP43 and TH in patients of different nationalities was compared. No statistical significance was observed in the protein expression of GAP43 and TH in patients of different nationalities in the sinus rhythm and AF groups. No difference was observed in the protein expressions of GAP43 and TH between Xinjiang Uygur and Han nationalities. Thus, neither the protein expression of GAP43 and TH in AF patients of Xinjiang Uygur and Han nationalities nor the distribution of the sympathetic nerve in the heart and the automatic nerve growth activity showed a nationality difference.

The difference in protein expression of GAP43 and TH in the sinus rhythm and AF groups was compared, with different nationalities used as the stratification factors. The results showed a statistical significance in the difference between the sinus rhythm and AF groups ($P < 0.05$). The difference in protein expressions of GAP43 and TH in patients with different ages was compared, with diseases used as the stratification factors. The results

showed that only the protein expression of GAP43 in patients with different ages in the AF group had statistical significance. Aging plays a vital role in the triggering and maintenance of AF.

The possible reasons why AF causes neural eruption and inhomogeneous distribution are as follows:

(1) Electrical remodeling and structure reconstruction (Miyauchi et al., 2003) during AF cause atrial enlargement, insufficient blood supply, and myocardial damage, which impair the nerve. GAP43 and β-NGF can help in neural development and neural recovery, which promote the regeneration of impaired nerves and promote the growth of the intact myocardial nerve.
(2) The atrial structure reconstruction in AF causes distribution disorder and the regeneration of nerve in the atria. ANS distribution density intensifies but not evenly. Therefore, the reconstruction of the vagus nerve is accompanied with the reconstruction of the sympathetic nerve (Sakamoto et al., 2010).
(3) AF causes myocardial ischemia. Neurohormones, such as cytokine and growth factor, which are increased in circulation, may be the cause of atrial neural development (Yang et al., 2011).

Conclusively, the reconstruction of the automatic nerve is closely related to AF. An imbalance in the automatic nerve could cause AF. Then, AF could cause the reconstruction of the automatic nerve, making AF maintenance easier. However, the exact mechanism that causes the reconstruction of the automatic nerve and electrical remodeling needs further exploration. We closely combined ANS with AF despite the fact that many blind zones are still present. The triggering and maintenance mechanism of AF will be further elucidated with in-depth studies on ANS. Reversing the reconstruction of the automatic nerve may be the new therapeutic target of AF, which will guide clinical treatment and improve the prognosis of patients with AF.

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