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ORIGINAL ARTICLE

Does education level protect us from rapid ageing? Sirtuin expression versus age and level of education

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Abstract

PURPOSE: SIR proteins (silent information regulators, sirtuins, SIRT1 – SIRT7, SIR1 – SIR7) belong to NAD^+-dependent deacetylases, enzymes taking part in a catalytic reaction of deacetylation, i.e. splitting the rest of acetic acid from protein substrates. Sirtuins play an important role in many cellular processes and are, therefore, involved in the ageing process and in the regulation of cell life. The aim of this paper is to verify the statistical hypothesis assuming the correlation between the age and level of education of examined persons and the expression of selected sirtuins (SIR1 – SIR7, SIRT1 – SIRT7) at the mRNA level in the Polish population.
MATERIAL AND METHODS: 197 people, aged M = 38.27 (SD = 13.19), in whom expression at the level of mRNA for SIR1 – SIR7 was determined, took part in the study (99 healthy people with a negative history of mental and somatic diseases and 98 people with diagnosed recurrent depressive disorders).
RESULTS: A significant correlation was found in the case of age of the examined individuals and the expression of SIR1 – SIR7 at the mRNA level ($p < 0.001$). Differences in the expression of SIR1 – SIR7 were also found in relation to the level of education (number of years of education) of the examined population ($p < 0.001$).
CONCLUSIONS: 1. The higher the number of years of education, the higher the level of SIR1 and SIR6 expression, and the lower the level of SIR2, SIR3, SIR4, SIR5 and SIR7 expression. 2. With age, the level of SIR1 and SIR6 expression decreases and the expression of SIR2, SIR3, SIR4, SIR5 and SIR7 increases.

Abbreaviations:
SIR proteins, SIRT1 – SIRT7, SIR1 – SIR7 - silent information regulators, sirtuins
M - mean
SD - standard deviation
RDD - recurrent depressive disorders

INTRODUCTION

Sirtuins (silent information regulators) are enzymes belonging to NAD^+-dependent histone deacetylases (Osborne *et al.* 2016; Stoh *et al.* 2017). They play an important role in both the central nervous system and the autonomous nervous systems (McGrory *et al.* 2018). They are

involved in changes related to neuroinflammation, neurodegeneration or mitochondrial dysfunctions (Imai & Guarente, 2016). Sirtuins regulate many functions of cellular metabolism (DNA repair, genome stability, inflammatory reaction, apoptosis, cell cycle, mitochondrial functions) (Wątroba & Szukiewicz, 2016). They are assigned a significant role in physiological ageing processes [6], as well as in the proper course of cognitive functions (Rizzi & Roriz-Cruz, 2018). Through engagement in cellular processes, such as transcription, apoptosis, inflammatory processes, post-translational protein modification, activation of DNA repair mechanisms or regulation of intracellular metabolic processes (Grabowska *et al.* 2017; van de Ven *et al.* 2017), sirtuins are involved in body ageing processes and in regulating cell life (Snyder-Warwick *et al.* 2018).

Reduced expression of sirtuins was confirmed in patients with diagnoses of mental disorders (in the course of a depressive episode in recurrent depressive disorders (McGrory *et al.* 2018), Alzheimer's disease (Rizzi & Roriz-Cruz, 2018; Hadar *et al.* 2018) (SIR1)) and somatic diseases, i.e. cardiovascular diseases (Pillai *et al.* 2010; Bindu *et al.* 2016; Sarikhani *et al.* 2018) (SIR2, SIR3), oncological diseases (SIR2) (McGlynn *et al.* 2014), metabolic diseases (Aditya *et al.* 2017; Lemos *et al.* 2017; Çalışkan *et al.* 2018) (SIR1, SIR2, SIR6), rheumatic disorders (Ailixiding *et al.* 2015), as well as in the people with the risk of obesity (SIR1 and SIR2) (Arab Sadeghabadi *et al.* 2018).

The aim of this paper is to verify the statistical hypothesis assuming a correlation between the age and level of education of the examined persons and the expression of selected sirtuins (SIR1 – SIR7, SIRT1 – SIRT7) at the mRNA level in the Polish population.

MATERIALS AND METHODS

Material

The selection of the subjects for the examined group was performed based on simple random sampling. All the subjects were native Poles from central Poland, not related to one another. The respondents decided to participate in the study after they had been informed of the purpose and ensured that their participation was voluntary, and the personal details and results of the tests conducted would not be distributed but used only and exclusively in general comparisons. Each patient gave written consent to participate in the experiment in accordance with the report approved by the Bioethics Committee of the Medical University of Lodz, approval No.: RNN/137/17/KB of 11/ 04/ 2017.

197 individuals took part in the research. Among them, there were 99 healthy people with a negative history of mental and somatic diseases (group A) and 98 people with diagnosed recurrent depressive disorders (RDD) treated at the Department of Adult Psychiatry of the Medical University of Lodz (group B). The study group included persons hospitalized psychiatrically for the first time and not treated earlier due to depressive disorders, as well as persons treated pharmacologically for many years, admitted to the unit in order to modify the therapy or due to deterioration of their health condition (another affective episode).

Methods

Determination of expression for SIR1 – SIR7 at the mRNA level

On the day of qualification for the experiment, samples of 10 ml of venous blood (two 5 ml test tubes) were collected from the participants of the study by qualified medical personnel using sterile, disposable equipment.

Total RNA isolation from the patients' blood was performed by TRIzol method in accordance with the procedure provided by the manufacturer. Dry sediments were dissolved in 30 µl of water free from RNases. Isolated RNA was stored in a temperature of -80°C. Total RNA quality was tested with Agilent RNA 6000 Nano Kit (Agilent Technologies) as recommended by the manufacturer. The quality of the isolated RNA was tested with 2100 Bioanalyzer (Agilent Technologies). The degree of total RNA degradation was determined with an electropherogram and RIN values obtained. Only the samples with RIN > 7 were subjected to further analysis.

Real-Time PCR reaction was conducted using TaqMan® Universal PCR Master Mix, No UNG (Applied Biosystems) according to the protocol provided by the manufacturer. The reaction mixture ratio was presented in the table. To calculate relative expression of miRNA genes, the Ct Livak 2001 comparative method was used. The level of SIRT1 gene expression in particular tissues was normalized in relation to the RPL13A reference gene.

An RT reaction was carried out using TaqMan® RNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's recommendations, using specific starters and Hs 01009006_m1, Hs 01560289_m1, Hs 00953477-m1, Hs 01015516_g1, Hs 00978331_m1, Hs 00966002_m1, Hs 01034683_g1, Hs01042796_m1, Hs04194366_g1 probes, respectively for SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, SIRT7, MMP 7 and RPL13A, delivered by Applied Biosystems.

RESULTS

The sociodemographic characteristics of the studied population are presented in Table 1.

Table 2 presents descriptive statistics for expression of SIR1 – SIR7 at the mRNA level.

Table 3 presents the results of the correlation analysis (Spearman's rank correlation) of the age of the examined individuals and the level of expression of SIR1 – SIR7 at the mRNA level. SIR1 and SIR6 expression decreased significantly with age of the subjects. In other cases, the relationship was positive.

Tab. 1. Characteristics of the studied group in terms of demographic features

Variable	*N* = 197	**Group A** *N* = 99	**Group B** *N* = 98
Women / men *n (%)*	135 / 62 (67.84 / 31.16)	65 / 34 (65.66 / 34.34)	70 / 28 (71.43 / 28.57)
Age *M (SD)*	38.27 (13.19)	27.37 (10.59)	47.27 (10.59)
	Education *n (%)*		
Vocational (11 years of education)	22 (11.17)	-	22 (22.68)
Secondary (12 years of education)	89 (45.18)	43 (43.43)	45 (46.39)
Higher (15 or 17 years of education)	86 (43.66)	56 (56.57)	30 (30.93)

Group A – subjects not treated psychiatrically or somatically; Group B – subjects treated for recurrent depressive disorders; M – mean; SD – standard deviation.

Tab. 2. Average standard deviation for SIR1 – SIR7

mRNA ($2^{-\Delta\Delta ct}$)	*N* = 197	**Group A** *N* = 99	**Group B** *N* = 98
SIR1 M (SD)	0.338 (0.301)	0.596 (0.182)	0.071 (0.051)
SIR2 M (SD)	0.198 (0.163)	0.061 (0.045)	0.339 (0.112)
SIR3 M (SD)	0.135 (0.091)	0.066 (0.048)	0.207 (0.065)
SIR4 M (SD)	0.125 (0.091)	0.047 (0.022)	0.206 (0.056)
SIR5 M (SD)	0.124 (0.084)	0.049 (0.018)	0.201 (0.046)
SIR6 M (SD)	0.214 (0.153)	0.353 (0.085)	0.073 (0.021)
SIR7 M (SD)	0.120 (0.079)	0.053 (0.022)	0.191 (0.051)

Group A – subjects not treated psychiatrically or somatically; Group B – subjects treated for recurrent depressive disorders; SIR1 – SIR7 – sirtuin 1 – sirtuin 7; M – mean; SD – standard deviation.

Table 4 contains the results of the Kruskal-Wallis ANOVA test for the following variables: education and SIR1 – SIR7 (N = 197). Statistically significant differences were observed for each of the analysed sirtuins ($p < 0.001$).

Due to the fact that all the persons with vocational education were treated with a diagnosis of RDD, in order to eliminate the influence of the disease on the obtained results, we conducted an additional analysis of the comparison of SIR1 – SIR7 expression level between persons with secondary and higher education in group A (N = 99) (Table 5). Statistical significance was observed only in the case of SIR1. The level of its expression was significantly higher among the examined individuals with higher education as compared to the subjects with secondary education. In the case of other sirtuins (except SIR4), higher expression rates were observed in the people with higher education. Therefore, apart from age of the subjects, the number of years of education (level of education) has a significant impact on the expression level of SIR1 – SIR7. However, as Tables 3 and 4 show, we obtained statistical significance in the case of analyses conducted for the entire group consisting of almost 200 individuals.

DISCUSSION

The direct relationship between sirtuin expression and longevity can be found in numerous studies: SIR1 (Giblin *et al.* 2014; Kilic *et al.* 2015; Wakeling *et al.* 2015; Kaszubowska *et al.* 2017), SIR2 (Fourcade *et al.* 2018), SIR3 (Doherty *et al.* 2017) or SIR6 (Hirvonen *et al.* 2017) and (Roichman *et al.* 2017) (research studies conducted based on the animal model)]. Even though Razzi *et al.* did not show any correlation between the expression of SIR1 and the age of the respondents (Razi *et al.* 2017) (1.309 people aged 70 and older were examined), yet the dependence of SIR1 expression on such factors as height, weight, percentage of fatty tissue in total body weight or cholesterol level was confirmed. Braidy *et al.* (2015) observed increased expression of SIR1 in the brains of tested animals with age, an increase in SIR2 protein level only in the occipital lobe, a significant decrease in SIR3, SIR4 and SIR5 expres-

Tab. 3. Correlation between age of the subjects and SIR1 – SIR7

mRNA ($2^{-\Delta\Delta ct}$)	*N* = 197		**Group A** *N* = 99		**Group B** *N* = 98	
	Spearman's Rho	*p*	Spearman's Rho	*p*	Spearman's Rho	*p*
SIR1 & age	-0.498	< 0.001*	0.471	< 0.001*	-0.092	0.374
SIR2 & age	0.613	< 0.001*	0.240	0.017*	-0.020	0.849
SIR3 & age	0.579	< 0.001*	0.292	0.003*	-0.008	0.939
SIR4 & age	0.579	< 0.001*	0.115	0.256	-0.105	0.306
SIR5 & age	0.635	< 0.001*	0.221	0.028*	0.048	0.641
SIR6 & age	-0.551	< 0.001*	0.075	0.461	-0.098	0.342
SIR7 & age	0.577	< 0.001*	0.024	0.815	-0.024	0.813

Group A – subjects not treated psychiatrically or somatically; Group B – subjects treated for recurrent depressive disorders; SIR1 – SIR7 - sirtuin 1 – sirtuin 7; * – statistically significant *p*, < 0,05

Tab. 4. Kruskal-Wallis ANOVA test by ranks for the following variables: education and SIR1 – SIR7 (*N* = 197).

mRNA ($2^{-\Delta\Delta ct}$)	**Vocational education** (11 years of education)	**Secondary education** (12 years of education)	**Higher education** (15 or 17 years of education)	***p***
	M (SD)	*M (SD)*	*M (SD)*	
SIR1	0.061 (0.018)	0.312 (0.283)	0.435 (0.311)	< 0.001*
SIR2	0.324 (0.124)	0.194 (0.161)	0.170 (0.161)	< 0.001*
SIR3	0.205 (0.066)	0.136 (0.095)	0.117 (0.084)	< 0.001*
SIR4	0.228 (0.057)	0.127 (0.091)	0.096 (0.077)	< 0.001*
SIR5	0.186 (0.038)	0.129 (0.089)	0.102 (0.102)	< 0.001*
SIR6	0.079 (0.020)	0.203 (0.152)	0.261 (0.261)	< 0.001*
SIR7	0.201 (0.031)	0.119 (0.081)	0.101 (0.101)	< 0.001*

SIR1 – SIR7 – sirtuin 1 – sirtuin 7; M – mean; SD – standard deviation; * - statistically significant *p*, < 0,05.

sion in the region of the hippocampus and frontal lobes with a simultaneous increase in SIR7 protein expression in the last of these areas of the brain. SIR6 expression was significantly reduced in all the examined structures. What is interesting, Okun *et al.* (2017) indicate increased neurogenesis in response to increased SIR6 expression in the hippocampus region.

There are not many studies evaluating the relationship between the expression of sirtuins and the level of education of the subjects, although, as mentioned above, sirtuins may be important for the proper cognitive functioning of a human being. Most definitely, sirtuins (especially SIR1) – through their involvement in antioxidant, anti-inflammatory and anti-apoptotic mechanisms, as well as in the processes that increase cerebral circulation and synaptic plasticity – promote cognitive efficiency (Cao *et al.* 2018). It is worth considering whether we are also dealing with reversed dependency – a higher level of education, through lifestyle modifications, favours increased expression of sirtuins slowing down the pace of ageing processes.

The influence of genetic factors on human life expectancy is estimated at between 5% and 35%; the rest includes environmental factors that shape epigenetic mechanisms (Robert & Labat-Robert, 2015) (modification of histones, DNA methylation or changes in gene expression). By integrating genetic and environmental factors, these mechanisms play an important role in the inheritance of neurobehavioural patterns and personality traits. This is done by preparing our bodies to cope with the rapidly changing environment. By means of increasing the chances of species survival by significantly shortening the time needed to pass on acquired skills to future generations, paradoxically in case of the environmental conditions changing too fast, epigenetic mechanisms may cause a lot of damage (Binder, 2018; Matosi *et al.* 2018). Therefore, a higher level of education, by changing lifestyle to a healthy one (diet, physical effort), may influence the expression of enzymes, including sirtuins. A modification of eating habits leads to a reduction of negative consequences of oxidative stress, improves mitochondrial functions, activates anti-inflammatory response, promotes neurogenesis, and increases synaptic plasticity. It also protects and prevents against age-related structural changes in the central nervous system (Dato *et al.* 2016) (Hadem *et al.* (2019) demonstrated a correlation between a change in eating habits and the level of sirtuins, while Franzoni *et*

Tab. 5. Comparisons of SIR1 – SIR7 expression levels between people with secondary and higher education in group A (*N* = 99).

mRNA ($2^{-\Delta\Delta ct}$)	**Secondary education** (12 years of education)	**Higher education** (15 or 17 years of education)	***Z***	***p***
SIR1 *M (SD)*	0.549 (0.181)	0.637 (0.175)	2.486	0.013*
SIR2 *M (SD)*	0.053 (0.021)	0.068 (0.056)	1.632	0.103
SIR3 *M (SD)*	0.056 (0.033)	0.074 (0.057)	1.483	0.138
SIR4 *M (SD)*	0.048 (0.023)	0.046 (0.022)	-0.330	0.742
SIR5 *M (SD)*	0.048 (0.018)	0.050 (0.018)	0.240	0.811
SIR6 *M (SD)*	0.339 (0.096)	0.362 (0.077)	1.087	0.277
SIR7 *M (SD)*	0.050 (0.019)	0.055 (0.025)	0.910	0.363

Group A – individuals not treated psychiatrically and somatically; SIR1 – SIR7 – sirtuin 1 – sirtuin 7; M – mean; SD – standard deviation; * - statistically significant p, < 0,05.

al. (2017) confirmed a relationship between increased physical activity and expression of SIR1 and SIR3 in the hippocampus region of rats).

To sum up, the obtained results not only confirm the importance of sirtuins for the functioning of the human body, but also emphasize the significance of epigenetic mechanisms for maintaining its positive quality.

CONCLUSIONS

1. The higher the number of years of education, the higher the level of SIR1 and SIR6 expression, and the lower the level of SIR2, SIR3, SIR4, SIR5 and SIR7 expression.
2. With age, the level of SIR1 and SIR6 expression decreases and the expression of SIR2, SIR3, SIR4, SIR5 and SIR7 increases.

STATISTICS

Selected methods of descriptive statistics and methods of statistical reasoning were used in the statistical analysis of the collected material. During statistical verification of the hypotheses, a two-tailed critical area was assumed.

Appropriate structural indicators, i.e. prevalence of a given trait expressed in percentage terms, were applied in the description of qualitative features in the examined group of affected patients and the control group. Arithmetic mean (M) was calculated to describe the value of average quantitative features. The range of the values (with the minimum and maximum values determined) as well as standard deviation (SD) were assumed as measures of dispersion.

The nature of the distribution of all variables was examined with the Shapiro–Wilk test. In relation to non-parametric variables, the non-parametric Mann-Whitney U-test (in case of two independent groups) and the Kruskal-Wallis ANOVA test (in case of three independent groups) were applied in statistical comparisons between the examined groups. Spearman's rank correlation coefficient was used to evaluate the correlations between the analysed variables.

The materiality level for all the statistical methods applied was set at $p < 0.05$ (Kirkwood and Sterne, 2003). All statistical calculations were conducted using computer software STATISTICA PL, version 13.1.

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