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Information entropy-based fitting of the disease trajectory of brain ischemia-induced vascular cognitive impairment★

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Abstract

The present study investigated the disease trajectory of vascular cognitive impairment using the entropy of information in a neural network mathematical simulation based on the free radical and excitatory amino acids theories. Glutamate, malondialdehyde, and inducible nitric oxide synthase content was significantly elevated, but acetylcholine, catalase, superoxide dismutase, glutathione peroxidase and constitutive nitric oxide synthase content was significantly decreased in our vascular cognitive impairment model. The fitting curves for each factor were obtained using Matlab software. Nineteen, 30 and 49 days post ischemia were the main output time frames of the influence of these seven factors. Our results demonstrated that vascular cognitive impairment involves multiple factors. These factors include excitatory amino acid toxicity and nitric oxide toxicity. These toxicities disrupt the dynamic equilibrium of the production and removal of oxygen free radicals after cerebral ischemia, reducing the ability to clear oxygen free radicals and worsening brain injury.

Key Words: vascular cognitive impairment; bilateral ligation of the common carotid artery; acetylcholine; nitric oxide synthase; free radical; glutamate

Abbreviations: VCI, vascular cognitive impairment; iNOS, inducible nitric oxide synthase; cNOS, constitutive nitric oxide synthase

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INTRODUCTION

Vascular cognitive impairment (VCI) is defined as cognitive damage induced or complicated by vessel factors. VCI can occur alone or accompany Alzheimer's disease[1]. VCI is reversible and its increasing incidence is making VCI a main disease in the elderly. VCI is categorized into two subtypes, vascular cognitive impairment no dementia and vascular dementia[2]. Previous studies mainly have focused on the pathogenesis of vascular dementia by investigating single indicator changes during VCI formation[3-4]. However, the factors involving the progression from brain ischemia to VCI, key time points, and the changes of those factors with time, *i.e.* the disease trajectory of VCI, rarely are reported. Before brain ischemia progresses to VCI is the optimal time to reverse and control VCI.

An artificial neural network is a large-scale, parallel nonlinear dynamical system composed of the connection of a simple "neuron". It has a strong ability of nonlinear operation, self-learning and fault tolerance to data input[5-6]. Entropy, which was first introduced by CE Shannon in information theory, is a concept in thermodynamics. Information theory has been used extensively in engineering and social economics[7]. In information theory, entropy is a measure of the uncertainty associated with a random variable, and information is a measure of the degree of system order. Their absolute values are equal but one is positive and the other is negative. Quantification of indicators is the quantitative assignment of the importance of different aspects of an evaluated object. That is, the greater the degree of variation for one indicator, the smaller the entropy is, the amount of information provided by the indicator is larger, and the weight of the indicator becomes more important[8].Therefore, during analysis, the weight of each indicator can be calculated through the use of information entropy according to the variation degree of indicators, followed by indicator weighting, to obtain objective evaluation results. The weight of indicators can be divided into subjective and objective methods, weighting according to different sources[9]. The subjective weighting method fully uses related knowledge and exhibits hereditability, but this method is relatively optional. The objective weighting method mainly focuses

on differences and the objectivity of indicators, but it cannot reflect the subjective intention of decision makers. In the objective weighting methods, entropy has been used frequently to calculate indicator weight, weight indicators and obtain objective evaluation results. This method is reliable, accurate, simple and scientific[10]. Compared to routine analysis methods, the present study quantitatively described and analyzed the correlation among influential factors using information entropy. This method can analyze multiple factors, avoid fuzzification and subjectivity, and enhance the objectivity of weighting. Moreover, this method has mathematic theoretical evidence and increases reliability.

The present study established a VCI model in rats by bilateral ligation of the common carotid artery to investigate the disease trajectory of VCI using information entropy in a neural network mathematical simulation.

RESULTS

Quantitative analysis of experimental animals

A total of 94 rats were used; 34 died due to acute brain ischemia. The remaining 60 rats were assigned to sham-surgery or injury groups according to body mass and learning and memory scores. The VCI model was obtained for the injury group by permanent bilateral ligation of the common carotid artery. These 60 rats were included in the final analysis.

Free radical- and excitatory amino acids-associated biochemical indicators in the brain tissues of VCI rats

Glutamate content was significantly increased in the brains of the injury group at 3 days after VCI compared with the sham-surgery group ($P < 0.01$), but gradually decreased with time, and returned to the normal level by 42 days ($P > 0.05$). Catalase, superoxide dismutase, and glutathione peroxidase content significantly decreased, but malondialdehyde significantly increased in the injury group compared with sham-surgery group ($P < 0.01$), indicating free radical injury in the VCI injury rats. Catalase and glutathione peroxidase remained unchanged in the injury group for 56 days following model establishment ($P > 0.05$), but superoxide dismutase continued to decrease and malondialdehyde content gradually increased with increasing time ($P < 0.05$ or $P < 0.01$, respectively).

The injury group rats exhibited significantly increased inducible nitric oxide synthase (iNOS) content compared with the sham-surgery group ($P < 0.05$) which gradually deceased over time ($P < 0.05$), and returned to the normal level at 56 days. iNOS content was significantly elevated, but constitutive nitric oxide synthase (cNOS) content was significantly decreased 3 days after VCI ($P < 0.01$). Acetylcholine content significantly declined in the brains of the injury group compared with the sham-surgery group ($P < 0.01$), indicating cholinergic system injury in the rat brains. Over prolonged time, acetylcholine content gradually decreased, with a significant difference at 28 days ($P < 0.05$ or $P < 0.01$), consistent with the time point phase of learning and memory function (Table 1).

The disease trajectory of VCI

All data were analyzed and fitted. A total of seven input fitting curves were obtained (Figure 1). A time fitting curve displayed that glutamate content significantly declined during 0–20 days, was stable from 20–33 days, significantly decreased again during 33–49 days, and increased during 49–56 days. Therefore, 20, 33, and 49 days were selected as the time inflexion points for glutamate. Catalase significantly reduced during 0–20 days, remained unchanged during 20–28 days, significantly decreased again during 28–52 days, and slightly increased during 52–56 days. Therefore, 20, 28 and 52 days were selected as the time inflexion points of catalase. Superoxide dismutase content significantly decreased during 0–49 days, and remained stable during 49–56 days, so the 49-day timepoint was regarded as the time inflexion point. During 0–49 days, malondialdehyde significantly elevated, before decreasing during 49–56 days, so the 49-day timepoint was regarded as the time inflexion point. Glutathione peroxidase and iNOS content continued to decrease during the experiment. cNOS content rapidly increased during 0–17 days, decreased during 17–30 days, increased during 30–49 days, and decreased during 49–56 days. Therefore, 17, 30 and 49 days were used as the time inflexion points.

According to the above analysis results, the time inflexion points of glutamate, malondialdehyde, catalase, superoxide dismutase, glutathione peroxidase, iNOS and cNOS were 17, 20, 28, 30, 33, 49 and 52 days, respectively, and 19, 30 and 49 days were primarily used when analyzing the influence of the above seven factors on output (Figure 1).

Bilateral ligation of the common carotid artery induces chronic brain ischemia and has been used as a model for studying VCI and evaluating drug efficacy[11-12]. Bilateral ligation of the common carotid artery-induced chronic brain ischemia can damage cholinergic neurons in the frontal cortex and hippocampus, which impairs learning and memory functions, and finally results in cognitive impairment at 6 weeks following model establishment[13-14]. In the present study, VCI formation was established at 42 days following injury. In early brain ischemia (0–19 days post ischemia), iNOS and glutamate exhibited the greatest influence on acetylcholine, *i.e.* the weight of iNOS and glutamate was maximum, and cNOS followed. In the middle-stage of ischemia, prior to VCI formation (19–30 days post ischemia), the influence of each indicator on acetylcholine remained unchanged (with the weight of superoxide dismutase maximum, and the weight of cNOS minimum). In the middle to late stage of ischemia (30–49 days post ischemia), the weight of malondialdehyde was maximum, while that of superoxide dismutase decreased. In the late stage of ischemia (49–56 days), *i.e.* following VCI formation, the weight of all indicators was similar except glutamate (Table 2).

Table 1 Glutamate, malondialdehyde, inducible nitric oxide synthase, acetylcholine, catalase, superoxide dismutase, glutathione peroxidase and constitutive nitric oxide synthase content in rat brain

Indicator	Day after ischemia					
	3	7	14	28	42	56
Glutamate (μmol/mg)						
Sham-surgery	75.96±8.49	77.57±7.77	75.24±8.58	76.16±6.97	77.53±7.69	76.09±9.88
Injury	120.66±13.08[a]	105.36±12.39[ac]	98.98±7.85[ac]	88.73±9.70[bce]	82.54±8.61[ceg]	80.29±10.30[ceg]
Catalase (U/mg)						
Sham-surgery	15.10±2.47	16.36±1.84	16.58±2.44	15.55±2.11	15.06±1.98	14.15±2.09
Injury	3.11±0.85[a]	2.85±0.63[a]	2.73±0.68[a]	2.59±0.43[a]	2.28±0.82[a]	2.12±0.71[a]
SOD (U/mg)						
Sham-surgery	131.49±10.17	130.56±9.82	130.71±13.60	128.94±12.40	129.41±13.61	124.61±11.96
Injury	79.75±8.11[a]	75.30±6.64[a]	64.88±5.87[ad]	49.84±6.02[acg]	41.83±6.40[acg]	41.20±4.84[acg]
MDA (nmol/mg)						
Sham-surgery	7.50±0.72	7.81±0.86	7.36±0.84	7.25±0.90	7.25±0.71	7.18±0.94
Injury	17.64±1.94[a]	18.50±1.50[a]	19.60±1.85[ad]	21.21±1.43[ac]	23.30±1.62[acgj]	23.02±1.71[acgj]
GSH-Px (U/mg)						
Sham-surgery	1 007.86±92.11	1 031.21±90.32	1 034.08±124.93	1 036.75±128.09	1 022.32±126.39	1 007.89±105.49
Injury	501.04±88.23[a]	500.64±78.15[a]	470.68±63.04[a]	454.49±50.81[a]	431.96±54.58[a]	420.24±41.10[a]
iNOS (U/mg)						
Sham-surgery	0.14±0.03	0.18±0.04	0.17±0.04	0.15±0.03	0.20±0.02	0.20±0.01
Injury	0.99±0.13[a]	0.83±0.06[ac]	0.72±0.13[acf]	0.54±0.08[aceg]	0.38±0.05[acegi]	0.22±0.04[cegik]
cNOS (U/mg)						
Sham-surgery	0.24±0.03	0.22±0.03	0.21±0.02	0.23±0.03	0.20±0.02	0.21±0.02
Injury	0.05±0.03[a]	0.12±0.03[ac]	0.14±0.07[ac]	0.15±0.03[bc]	0.16±0.01[c]	0.17±0.03[cegik]
Acetylcholine (μg/mg)						
Sham-surgery	1 462.31±129.31[a]	1 426.92±127.40	1 432.72±149.88	1 459.69±147.55	1 366.15±141.78	1 357.69±143.72
Injury	1 004.62±118.44[a]	985.49±132.05[a]	933.85±120.78[a]	852.62±120.78[ad]	752.42±92.41[aceh]	738.31±79.28[aceg]

Data were expressed as the mean ± SD of five rats in each group at each time point. Paired comparison between groups was conducted using the least significant difference-*t* method. [a]$P < 0.01$, [b]$P < 0.05$, *vs*. sham-surgery group; [c]$P < 0.01$, [d]$P < 0.05$, *vs*. 3 days; [e]$P < 0.01$, [f]$P < 0.05$, *vs*. 7 days; [g]$P < 0.01$, [h]$P < 0.05$, *vs*. 14 days; [i]$P < 0.01$, [j]$P < 0.05$, *vs*. 28 days; [k]$P < 0.01$, *vs*. 42 days. SOD: Superoxide dismutase; MDA: malondialdehyde; GSH-Px: glutathione peroxidase; iNOS: inducible nitric oxide synthase; cNOS: constitutive nitric oxide synthase.

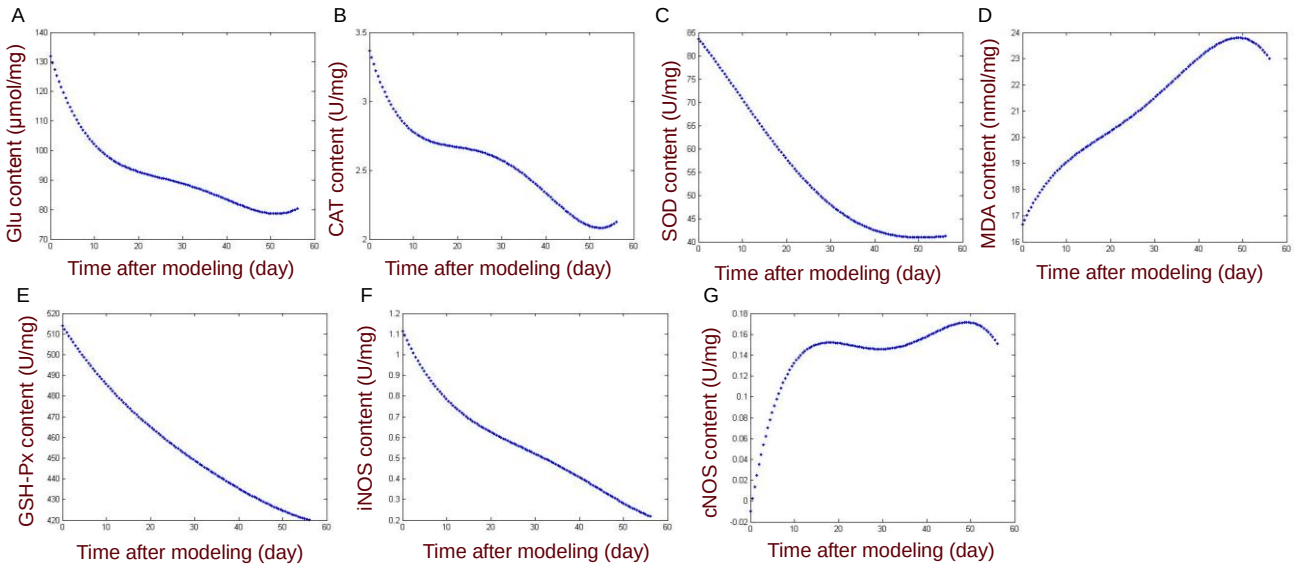

Figure 1 The fitting curves of glutamate (A), catalase (B), superoxide dismutase (C), malondialdehyde (D), glutathione peroxidase (E), inducible nitric oxide synthase (iNOS; F) and constitutive nitric oxide synthase (cNOS; G) content in the brain of rats with vascular cognitive impairment.

Sample data of each factor were fitted using Matlab software to obtain the fitting curves of these seven factors. The time inflexion points of glutamate, malondialdehyde, catalase, superoxide dismutase, glutathione peroxidase, iNOS and cNOS were 17, 20, 28, 30, 33, 49 and 52 days, respectively.

Glu: Glutamate; CAT: catalase; SOD: superoxide dismutase; MDA: malondialdehyde; GSH-Px: glutathione peroxidase.

Table 2 The weights of glutamate, malondialdehyde, inducible nitric oxide synthase (iNOS), catalase, superoxide dismutase, glutathione peroxidase and constitutive nitric oxide synthase (cNOS) at different time stages

Time after ischemia (day)	Glutamate	Catalase	Superoxide dismutase	Malondialdehyde	Glutathione peroxidase	iNOS	cNOS
0–19	0.233 3	0.037 6	0.069 7	0.131 6	0.135 6	0.240 4	0.151 7
19–30	0.172 6	0.060 7	0.264 2	0.177 9	0.194 8	0.112 1	0.017 8
30–49	0.173 4	0.144 3	0.067 7	0.330 3	0.095 8	0.097 0	0.091 4
49–56	0.042 2	0.139 0	0.227 7	0.138 5	0.201 9	0.110 9	0.139 7

The weight is the relative importance degree of one indicator in the total evaluation, representing the quantitative assignment of the importance of different factors in one evaluated objective.

DISCUSSION

Memory synapses are cholinergic synapses, and the cholinergic pathway constructs the memory trace[15]. Therefore, cholinergic functional changes are closely correlated with learning and memory[16]. In addition, environment, diet and other objective factors can also influence learning and memory[17]. Therefore, the present study used acetylcholine as the terminal evaluation indicator to represent the output of the mathematic model, replacing learning and memory results. This allows consistency of conditions in all indicators and prevents individual differences in learning and memory results. Our results from the present study suggested that in the early brain ischemia induced by bilateral ligation of the common carotid artery, the weight of glutamate and nitric oxide synthase was maximum. These data indicate excitatory amino acid toxicity in the brain of VCI rats, consistent with previous results[18-19]. In addition, nitric oxide synthase participates in brain ischemia by producing nitric oxide in the early stage of brain ischemia[20]. iNOS exhibited toxicity after brain ischemia. cNOS includes neuronal nitric oxide synthase and endothelial nitric oxide synthase. The endothelial nitric oxide synthase can protect the brain by maintaining regional cerebral blood flow[21]. In the present study, the weight of iNOS was slightly greater than cNOS, suggesting that in early brain ischemia, nitric oxide synthase mainly exhibits toxic effects by iNOS, with some accompanying cerebroprotection by cNOS. With prolonged brain ischemia, the influence of glutamate and nitric oxide synthase on VCI formation decreased, but their weight in oxidative stress-related corresponding enzymes increased. In the middle stage of ischemia, the weight of oxidative stress reached a peak; in the middle and late stage, the weight of malondialdehyde was maximum. These dynamic changes were consistent with the clearance of oxygen free radicals[22], indicating that oxidative stress injury exists throughout the process from brain ischemia to VCI formation. After brain ischemia, superoxide dismutase content in the brain tissue decreased, and reached a minimal level at 19 days, which reduced the brain's ability to clear oxygen free radicals. With decreasing superoxide dismutase content, the production of oxygen free radicals increased, malondialdehyde began to accumulate, and the injury to brain tissues worsened. VCI formed at this time. Therefore, VCI formation is a multifactorial process. Excitatory amino acids toxicity and nitric oxide toxicity after ischemia damaged the balance of the production and clearance of oxygen free radicals, reduced the clearance of oxygen free radicals, aggravated brain injury, and resulted in VCI when the brain injury reached the severest condition.

MATERIALS AND METHODS

Design

A randomized, controlled, animal experiment.

Time and setting

The experiment was performed at the Laboratory of Pharmacology, Harbin University of Commerce, China from April to December 2010.

Materials

A total of 94 healthy adult male Sprague-Dawley rats, aged 30–32 weeks, weighing 300–350 g, were provided by the Laboratory Animal Center of Heilongjiang University of Chinese Medicine (No. 0102007). The animals were housed at 20–25°C, with a relative humidity of 40–70%, in a 12-hour day/night cycle. Experimental protocols were performed in accordance with the *Guidance Suggestions for the Care and Use of Laboratory Animals*, issued by the Ministry of Science and Technology of China[23].

Methods

VCI model establishment

The VCI model was established by permanent bilateral ligation of the common carotid artery[24]. The injury group was deprived of food prior to ligation, anesthetized with chloral hydrate, and placed in a supine position. The left and right common carotid artery were separately ligated using 0# silk suture, and the incision was sutured layer by layer. The sham-surgery group was not subjected to ligation of common carotid artery but underwent anesthesia and had a surgical incision made.

Preparation of the right hemisphere homogenate

Five rats from each group were selected at 3, 7, 14, 28, 42, and 56 days following model establishment, anesthetized by 3% chloral hydrate (Shanghai Chemical Reagent Company, No. 060707), and sacrificed. The brain was rapidly harvested in an ice dish, and washed in

normal saline at 0–4°C after the brain stem and cerebellum were removed. The samples were dried using filter paper, and the right hemisphere was stored in liquid nitrogen. The right hemisphere was subsequently weighed and rapidly placed in a pre-cooled glass homogenizer (SK-1, Jintan Medical Instrument, Jiangsu Province, China), mixed with cold normal saline at a mass volume ratio of 1:9, homogenized at 0–4°C before being centrifuged at 2 000 r/min, for 10 minutes at 4°C. The serum was harvested for detection.

Determination of glutamate, malondialdehyde, catalase, superoxide dismutase, glutathione peroxidase, iNOS and cNOS content in the right hemisphere

The serum of the brain tissue homogenate was harvested, and glutamate[25], malondialdehyde[26], catalase[27], superoxide dismutase[28], glutathione peroxidase[29], iNOS and cNOS[30] content were determined using an ultraviolet spectrophotometer (WFZ UV-2102C, Unico (Shanghai) Instrument, Shanghai, China) according to the manufacturer's instructions.

Determination of acetylcholine content in the right hemisphere

Acetylcholine content in the right hemisphere was determined using a double antibody sandwich enzyme-linked immunosorbent assay[31] according to the kit's instructions. Absorbance at 450 nm was measured using a microplate reader (RT-6000, Shenzhen Rayto Life Science Stock Co., Ltd., Guangdong Province, China). Unary linear regression equations and standard curves were established based on the content and absorbance of the standard which was used to calculate the concentrations of the samples.

The establishment of a simulation model of the VCI trajectory

For data analyses and time inflexion points, the values of glutamate, malondialdehyde, acetylcholine, catalase, superoxide dismutase, glutathione peroxidase, iNOS and cNOS for each rat were used as independent variables to establish a gray scale correlation[32]. The initialized image of each number sequence was calculated, and the absolute difference of each point was obtained, followed by the maximal and minimal differences between the two points. The correlation coefficient was calculated according to the formula (1):

$$\gamma_{0i}(k)=\frac{\Delta_{\min}+\xi\Delta_{\max}}{\Delta_i(k)+\xi\Delta_{\max}},\quad k=1,\cdots 7, i=1\cdots n \qquad (1)$$

Where ξ is a discrimination coefficient and $\xi\in(0,1)$. This value is used to attenuate the influence of the distortion induced by absolute differences that are too big, to improve the significance of the differences among correlation coefficients.

The correlation degrees of each independent variable (glutamate, malondialdehyde, catalase, superoxide dismutase, glutathione peroxidase, iNOS and cNOS content) and the dependent variable acetylcholine were calculated according to the formula (2), and the correlation degree was normalized. Fitting curves were made using Matlab software (Mathworks, Natick, MA, USA) and the time inflexion point of every indicator was analyzed and confirmed.

$$\gamma_{0k}=\frac{1}{n}\sum_{i=1}^{n}\gamma_{0i}(k), k=1,\cdots 7 \qquad (2)$$

Weight was calculated according to information entropy-based weighing method[33]. The corresponding sample data of seven independent variables were used as the neural network input, and the results of the corresponding samples determined the neural network output to design the neural network. Only one factor was changed and was regarded as the minimal value during that time period; the other factors remained unchanged as the neural network input. The neural network output was calculated using the neural network, and compared with the determined neural network output. The mean value of error was calculated. A decision matrix was obtained using the normalization method: $\dot{A}=(\dot{a}_{i,j})_{5\times 7}$. According to the decision matrix, error information entropy of the system was calculated as:

$$E_j=-\frac{1}{\ln n}\sum_{i=1}^{n}r_{i,j}\ln r_{i,j}, n=5, j=1\sim 7 \qquad (3)$$

The weight was calculated according to the entropy:

$$w_j=\frac{1-E_j}{\sum_{1}^{m}(1-E_j)} \qquad (4)$$

Statistical analysis

The data were expressed as the mean ± SD and analyzed using SPSS 17.0 for Windows (SPSS, Chicago, IL, USA) with one-way analysis of variance. Intergroup differences were compared by the least significant difference *t*-test. A value of $P < 0.05$ indicated a significant difference, and a value of $P < 0.01$ indicated a highly significant difference.

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Conflicts of interest: None declared.

Ethical approval: This study received permission from the Animal Ethics Committee of the Harbin University of Commerce, China.

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