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Analysis of differentially expressed genes related to cerebral ischaemia in young rats based on the Gene Expression Omnibus database

Yu Xia, Han Liu, Rui Zhu

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Abstract

BACKGROUND

The incidence rate of cerebral infarction in young people is increasing day by day, the age of onset tends to be younger, and its internal pathogenesis and mechanism are very complicated, which leads to greater difficulties in treatment. Therefore, it is essential to analyze the key pathway that affects the onset of cerebral infarction in young people from the perspective of genetics.

AIM

To compare the differentially expressed genes in the brain tissue of young and aged rats with middle cerebral artery occlusion and to analyse their effect on the key signalling pathway involved in the development of cerebral ischaemia in young rats.

METHODS

The Gene Expression Omnibus 2R online analysis tool was used to analyse the differentially expressed genes in the GSE166162 dataset regarding the development of cerebral ischaemia in young and aged groups of rats. DAVID 6.8 software was further used to filter the differentially expressed genes. These genes were subjected to Gene Ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis to determine the key gene pathway that affects the occurrence of cerebral ischaemia in young rats.

RESULTS

Thirty-five differentially expressed genes (such as *Igf2*, *Col1a2*, and *Sfrp1*) were obtained; 73 GO enrichment analysis pathways are mainly involved in biological

processes such as drug response, amino acid stimulation response, blood vessel development, various signalling pathways, and enzyme regulation. They are involved in molecular functions such as drug binding, protein binding, dopamine binding, metal ion binding, and dopamine neurotransmitter receptor activity. KEGG pathway enrichment analysis showed a significantly enriched pathway: The cyclic adenosine monophosphate (c-AMP) signalling pathway.

CONCLUSION
The c-AMP signalling pathway might be the key pathway in the intervention of cerebral infarction in young people.

Key Words: Gene Expression Omnibus database; Cerebral infarction in young people; Rats; Differential gene enrichment analysis; Pathway

Core Tip: This study mainly used the analysis technology related to biogenetic informatics to retrieve the samples of young cerebral ischemia rats from the authoritative global Gene Expression Omnibus database, identified the differential genes related to the onset of cerebral ischemia in young rats through the differential gene analysis method, further carried out Gene Ontology function enrichment analysis and Kyoto Encyclopedia of Genes and Genomes function enrichment analysis, and finally obtained the key gene pathway that affects ischaemic stroke in young rats. The findings provide clues for further realizing the transformation of basic medicine into clinical practical application, so as to finally realize the precise target intervention of young people with ischemic stroke and reduce the disability rate and mortality rate.

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INTRODUCTION

Cerebral infarction has the characteristics of a high disability rate, high mortality rate, and high recurrence rate. It has been the second leading cause of death in the world and seriously endangers human health. With rapid economic and social development, the incidence of cerebral infarction in young people is gradually increasing, and the age of onset tends to be younger. Compared with cerebral infarction in elderly individuals, the aetiology of cerebral infarction in young people is more diversified, which leads to certain difficulties in diagnosis and treatment. Studies have shown that there are approximately 2 million new young people with cerebral infarction every year in the world, but its treatment methods and effects are still limited[1]. Young people are the backbone of the family, society, and even the country. Once disabled, they will cause considerable damage to society and family.

The Gene Expression Omnibus (GEO) database is a public gene expression database created and maintained by National Center for Biotechnology Information in the United States in 2000. It contains a large amount of gene expression data, such as next-generation sequencing data, chip sequencing, and single-cell sequencing (including rich human clinical data and various animal model data). To find suitable intervention targets and more reasonable and effective treatment methods, we analysed the gene chip data of young cerebral infarction rats and old infarcted rats in the GEO database to identify the key gene pathways that distinguish these groups from one another.

MATERIALS AND METHODS

Selection of subjects

The GEO database (http://www.ncbi.nlm.nih.gov/geo) was searched with the key word "middle cerebral artery occlusion (MCAO)", the deadline was September 2022, and the GSE166162 dataset of the brain tissue of rats in the young MCAO group and the aged MCAO group was downloaded. The GSE166162 dataset included male rats aged 3-4 mo and weighing 340-400 g and male rats aged 18-20 mo and weighing 585-685 g. In this study, the gene chip data of brain tissue was identified according to the principles of rat grouping, age, sampling site, sex, and strain to avoid the influence of differential genes on other factors. Male SD rats aged 3-4 mo and male SD rats aged 18-20 mo were used as the research

subjects, and the brain tissue was used as the sampling site. Finally, three rat samples in the young MCAO group were numbered GSM5065037, GSM5065038, and GSM5065039, and three rat samples in the aged MCAO group were numbered GSM5065040, GSM5065041, and GSM5065042 (Table 1).

Differential gene analysis

The GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r) online analysis tool was used to perform differential gene analysis on the GSE166162 dataset. With logFC absolute value ≥ 1 and $P < 0.05$ as screening conditions, the differentially expressed genes in the brain tissue of the young MCAO group rats and the aged MCAO group rats were selected. In addition, up- and down-regulated genes significantly regulated in young cerebral ischaemia rats were screened out by adjusting *P* values.

Statistical analysis

To explain the pathways affected by differential genes in the brain tissue of cerebral infarction rats, all the differentially expressed genes were introduced into DAVID 6.8 (https://david.ncifcrf.gov/) for Gene Ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The overall analysis idea and specific analysis steps of this study are shown in a flow chart (Figure 1).

RESULTS

Differential gene analysis

Using GEO2R to conduct differential gene analysis on the GSE166162 dataset, 35 differentially expressed genes were obtained. Among them, 25 were upregulated with positive logFC, and 12 with negative logFC were downregulated (Tables 2 and 3). In addition, the significantly upregulated and downregulated genes were further screened after adjusting the *P* value with volcano maps (Tables 4 and 5). A volcano map can visually display red upregulated genes and blue downregulated genes (Figure 2). The above methods were used to discern related genes that could play a key role in the pathogenesis of cerebral infarction in young rats. The abnormal expression of these genes might affect biochemical processes, molecular functions, and related gene pathways in rats.

GO functional enrichment analysis

The DAVID 6.8 online analysis tool was used to perform GO functional enrichment analysis on the above 35 differentially expressed genes, and 111 GO items were obtained. With $P < 0.05$ as a significant enrichment criterion, 73 pathways were obtained. Among them, 54 (48.65%) were enriched in biological processes, including drug response, amino acid stimulation response, vascular development, various signalling pathways, enzyme regulation, and other biological processes; 10 (9.01%) were enriched in cell composition, mainly including the extracellular matrix, collagen trimer, and troponin complex; and 9 (8.11%) were enriched in molecular functions, mainly including drug binding, protein binding, dopamine binding, metal ion binding, and dopamine neurotransmitter receptor activity (Table 6).

KEGG pathway enrichment analysis

Using the DAVID 6.8 online analysis tool, the KEGG pathway enrichment analysis was performed on the 35 differentially expressed genes, and a total of seven pathways were enriched. With $P < 0.01$ as the significant enrichment criterion, a significant enrichment pathway was obtained. This pathway is the cyclic adenosine monophosphate (c-AMP) signalling pathway (Table 7).

DISCUSSION

Cerebral infarction is an important cause of disability and death worldwide. Although traditionally considered a disease of elderly individuals, infarction in young people is increasingly a global public health problem, and the average age of stroke onset is gradually decreasing. The incidence of infarction and hospitalization rates are increasing among young people in some countries[1]. The infarction in young people is generally considered to be different from that in older patients in terms of genetic pathogenesis, and its onset is a complex process of multigene and multipathway interactions, which is an important reason for the difficulty in treating the disease[2,3]. Therefore, revealing the pathogenesis of ischaemic infarction in young people at the molecular level has become a research hotspot in the treatment of this disease. In this study, suitable young rats with ischaemic infarction were selected from the Gene Expression Omnibus database as the research subjects, and biological gene chip technology was used to identify important genetic pathways to intervene and reduce the incidence of ischaemic infarction in young people to the greatest extent.

Table 1 Sample information

Sample number	Strain	Gender	Rat age	Grouping	Sampling site
GSM5065037	SD rat	Male	March-April	Young MCAO	Brain tissue
GSM5065038	SD rat	Male	March-April	Young MCAO	Brain tissue
GSM5065039	SD rat	Male	March-April	Young MCAO	Brain tissue
GSM5065040	SD rat	Male	Eighteen-twenty months	Aged MCAO	Brain tissue
GSM5065041	SD rat	Male	Eighteen-twenty months	Aged MCAO	Brain tissue
GSM5065042	SD rat	Male	Eighteen-twenty months	Aged MCAO	Brain tissue

MCAO: Middle cerebral artery occlusion.

Table 2 Upregulated differential genes in young infarcted rats

ID	*P* value	t	B	logFC	Gene symbol
1367571_at	0.00000058	13.77	4.3557	1.55	Igf2
1387854_at	0.0000015	12.2	3.9423	1.714	Col1a2
1370155_at	0.00000306	11.14	3.5959	2.022	Col1a2
1371861_at	0.00000562	10.29	3.2741	1.547	Sfrp1
1374172_at	0.00001368	9.16	2.7581	1.51	Col8a2
1367592_at	0.00001669	8.92	2.6355	1.732	Tnnt2
1390450_at	0.00002515	8.45	2.3752	1.266	LOC100910855Ogn
1372299_at	0.00003639	8.03	2.1313	1.003	Cdkn1c
1392510_at	0.00004648	7.77	1.9652	1.255	Fam180a
1370391_at	0.0001211	6.81	1.2813	1.393	LOC100911902Crabp2
1370956_at	0.00012686	6.76	1.2468	1.051	Dcn
1390532_at	0.00014662	6.62	1.1385	1.399	Slc13a4
1388116_at	0.00016115	6.54	1.0672	1.085	Col1a1
1387197_at	0.00024297	6.16	0.7521	1.139	Omd
1370959_at	0.00052678	5.49	0.1359	1.321	Col3a1
1367700_at	0.00057972	5.42	0.0577	1.054	Fmod
1385248_at	0.00072166	5.24	-0.1224	2.301	LOC100910855Ogn
1385486_at	0.00072866	5.23	-0.1304	1.026	Bnc2
1367847_at	0.00093931	5.03	-0.3419	1.163	Nupr1
1373148_at	0.00122143	4.82	-0.5632	1.146	Cpxm2
1387306_at	0.00144695	4.69	-0.7073	1.666	Egr2
1390835_at	0.00176986	4.54	-0.8798	1.239	Slc47a1
1383263_at	0.00179702	4.53	-0.8929	1.539	LOC100910855Ogn

Studies have found that the collagen type I alpha 2 (*COL1A2*) gene, which is a susceptibility gene of collagen-related diseases such as systemic sclerosis, contains a specific combination of two dinucleotide repeats and is involved in the regulation of gene expression. The *COL1A2* gene overaccumulates in affected organs or tissues, eventually leading to a systemic inflammatory immune response that causes damage to blood vessels in infarcts in young patients[4,5]. The above findings suggest that *COL1A2* may be closely related to ischaemic cerebrovascular diseases, such as vascular inflammation caused by systemic immune system abnormalities. This study is the first to find that *COL1A2* is associated with ischaemic stroke in young adults, which suggests that *COL1A2* could be modulated to reduce vascular inflammation and stabilize the vascular intima, thereby avoiding thrombus aggregation caused by

Table 3 Downregulated differential genes in young infarcted rats

ID	*P* value	t	B	logFC	Gene symbol
1374503_at	0.00000136	-12.35	3.9877	-1.314	Pbx3
1395359_at	0.00000867	-9.73	3.0291	-1.084	-
1390783_at	0.00001389	-9.14	2.7485	-1.025	Abca8a
1390052_at	0.00007757	-7.24	1.606	-1.015	LOC100912140
1373250_at	0.00008716	-7.13	1.5221	-1.12	Anln/Anlnl1
1396833_at	0.00067817	-5.29	-0.0711	-1.105	-
1368708_at	0.00068945	-5.27	-0.0847	-1.475	Drd2
1386931_at	0.00105762	-4.93	-0.4415	-1.465	Tnni3
1383516_at	0.00229766	-4.35	-1.1053	-1.138	Fgl2
1368478_at	0.00264936	-4.25	-1.2292	-1.061	Drd1
1368300_at	0.00271339	-4.23	-1.25	-1.206	Adora2a
1383578_at	0.00295369	-4.17	-1.3241	-1.017	LOC100911267Rad51

Table 4 Top 6 differentially up-regulated genes in young infarcted rats after adjustment of *P* value

ID	Adjusted *P* value	t	B	logFC	Gene symbol
1367571_at	0.0156	13.77	4.3557	1.55	Igf2
1387854_at	0.0156	12.2	3.9423	1.714	Col1a2
1370155_at	0.0238	11.14	3.5959	2.022	Col1a2
1371861_at	0.0291	10.29	3.2741	1.547	Sfrp1
1374172_at	0.0432	9.16	2.7581	1.51	Col8a2
1367592_at	0.0472	8.92	2.6355	1.732	Tnnt2

Table 5 Top 5 differential genes downregulated in young infarcted rats after adjustment of *P* value

ID	Adjusted *P* value	t	B	logFC	Gene symbol
1374503_at	0.0156	-12.35	3.9877	-1.314	Pbx3
1387450_at	0.0257	-10.71	3.4396	-0.922	Tgfa
1395359_at	0.0365	-9.73	3.0291	-1.084	-
1367695_at	0.0365	-9.63	2.9826	-0.976	Qdpr
1390783_at	0.0432	-9.14	2.7485	-1.025	Abca8

Two of the top 6 differentially expressed genes after adjustment of the *P* value were duplicated, and one of the top five downregulated differential genes was unnamed.

vascular intimal injury. From the perspective of the c-AMP pathway, the increase in the c-AMP concentration could inhibit the migration and intimal hyperplasia of vascular smooth muscle cells (VSMCs), promote the degradation of type I collagen by lysosomes, and reduce the content of type I collagen secreted into and out of VSMCs to protect them[6]. Collagen type VIII alpha 2 (*COL8A2*) is a protein-coding gene that encodes the α2 chain of type VIII collagen, a component of the vascular endothelium, which is responsible for the migration of VSMCs. It is necessary for proliferation and thus plays an important role in maintaining vessel wall integrity and structure[7]. This indicates that *COL8A2* is similar to *COL1A2*, and regulation of *COL8A2* can also reduce the incidence of stroke in young adults. It has been reported in the past that tumour necrosis factor-α (TNF-α) is an important proinflammatory cytokine secreted by vascular endothelial cells that mediates the production of many inflammatory mediators. Increased TNF-α is an independent risk factor for acute cerebral infarction, which is consistent with the conclusion of this study[8]. The systemic inflammatory immune response may play a

Table 6 Gene Ontology functional enrichment analysis of differential genes in young infarcted rats

GO	GO entry	GO description	Number of genes	*P* value
Biological process	GO:0042493	Drug reaction	6	5.21E-04
	GO:0001975	Response to amphetamine	3	0.001644593
	GO:0001568	Vascular development	3	0.003764749
	GO:0071230	Cellular response to amino acid stimulation	3	0.00430878
	GO:0006469	Negative regulation of protein kinase activity	3	0.007534713
	GO:0010579	Positive regulation of adenylate cyclase activity involved in G protein-coupled receptor signalling	2	0.01174588
	GO:0060158	Phospholipase C activates the dopamine receptor signalling pathway	2	0.01174588
	GO:0007212	Dopamine receptor signalling pathway	2	0.022075774
	GO:1900273	Positive regulation of long-term synaptic potentiation	2	0.023359725
	GO:0070208	Protein heterotrimer	2	0.025922792
	GO:0007190	Activation of adenylate cyclase activity	2	0.028479424
	GO:0051968	Positive regulation of glutamatergic synaptic transmission	2	0.033573445
	GO:0051482	Positive regulation of G protein-coupled cytosolic calcium concentration by phospholipase C activation	2	0.039905051
	GO:0048147	Negative regulation of fibroblast proliferation	2	0.043684948
Cellular composition	GO:0031012	Extracellular matrix	9	4.60E-10
	GO:0005578	Protein, extracellular matrix	7	5.09E-07
	GO:0005581	Collagen trimer	4	5.47E-05
	GO:0005584	Type I collagen trimer	2	0.002482326
	GO:0005861	Troponin complex	2	0.009893989
Molecular function	GO:0004952	Dopamine neurotransmitter receptor activity	2	0.006291172
	GO:0008144	Drug combination	3	0.00881302
	GO:0005515	Protein binding	7	0.011558726
	GO:0035240	Dopamine binding	2	0.013790827
	GO:0046872	Metal ion binding	6	0.025540723

For the convenience of typesetting, Table 6 only shows the enrichment analysis results of some important GO functions. GO: Gene Ontology.

very important role in the pathogenesis of stroke in young people, and it is worthy of further exploration.

Previous studies have confirmed that the secreted frizzled related protein 1 gene is a genetic predisposition gene for large atherosclerotic cerebral infarction, which is consistent with the results of this study[9]. Therefore, young people with high risk for ischaemic stroke (such as long-term hypertension, heavy smoking, and severe abdominal obesity) are genetically tested to screen out high-risk stroke patients who carry this susceptibility gene to minimize stroke morbidity. Studies have shown that insulin-like growth factor 2 (IGF2) is abundantly expressed in the central nervous system, and its deficiency is closely related to neuropsychiatric diseases such as vascular dementia[10]. This suggests that severe deficiency of IGF2 may cause the repeated occurrence of strokes in such patients, which in turn leads to a stepwise aggravation of the condition of patients with vascular cognitive impairment and eventually leads to the occurrence of diseases such as vascular dementia. This is also a scientific proposition worthy of in-depth exploration. Studies have shown that elevated serum troponin T is a predictor of poor prognosis in acute stroke, and elevated troponin T concentrations are associated with an increased risk of death in hospitalized patients, which is consistent with the findings of this study [11]. Therefore, in addition to paying attention to the common haematological risk factors for stroke in young people, clinicians also need to pay attention to troponin T, an indicator of cardiac injury. Preleukaemia transcription factor 3 (PBX3) and ATP-binding cassette transporter subfamily A member 8 (ABCA8) have been reported in malignant tumours. They play a key role in the pathogenesis of cancer, and high levels of PBX3 and ABCA8 are closely associated with poor prognosis in cancer patients. Their

Table 7 Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of differential genes in young infarcted rats

Entry	Patheway name	Number of genes	*P* value
rno04024	c-AMP signalling pathway	4	0.005710593
rno04512	ECM receptor interactions	3	0.012428441
rno04974	protein digestion and absorption	3	0.012428441
rno05146	amebiasis	3	0.019228955
rno04611	platelet activation	3	0.027273273
rno05012	Parkinson's disease	3	0.033955639
rno05034	alcoholism	3	0.044367858

c-AMP: Cyclic adenosine monophosphate; ECM: Extracellular matrix.

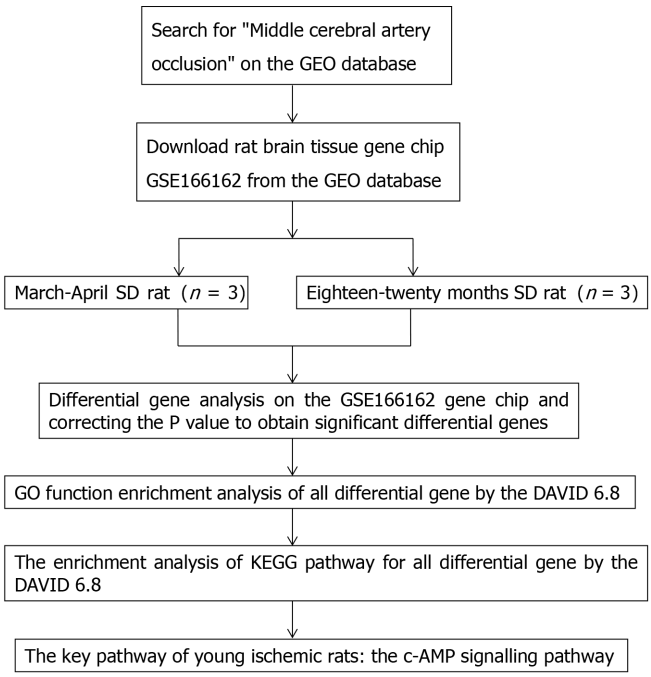

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Figure 1 Flow chart of the paper analysis ideas. GEO: Gene Expression Omnibus; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; c-AMP: Cyclic adenosine monophosphate.

association with tumorigenesis indirectly suggests that they may contribute to a hypercoagulable state in normal young patients, leading to thrombosis and eventual stroke[12,13]. This indicates that genes regulating tumorigenesis may be involved in the pathophysiological process of cerebral infarction, which is worthy of further exploration. Quinoid dihydrobiopterin is reduced to tetrahydrobiopterin under the action of quinoid dihydropteridine reductase (QDPR). Tetrahydrobiopterin can affect the vascular endothelium in various ways to promote the occurrence and development of cardiovascular and cerebrovascular diseases. For example, tetrahydrobiopterin deficiency can promote atherosclerosis and the production of oxygen free radicals[14]. This suggests that QDPR may play an important role in the pathogenesis of young infarcts. Based on the above findings, we speculate that atherosclerosis may also play an important role in the incidence of stroke in young adults, especially those after the age of 35 with poor diet and living habits (because they may have a higher proportion of diseases such as hypertension).

In addition, we obtained 73 significantly enriched pathways after GO functional enrichment analysis, of which 54 were significantly enriched in biological processes including drug reactions, various signalling pathways, enzyme regulation, and other biological processes; ten were significantly enriched with a focus on cell composition, mainly including the extracellular matrix, collagen trimer, troponin complex, *etc.*; nine were significantly enriched in molecular functionds, mainly including drug binding, protein binding, dopamine binding, and dopamine neurotransmitter receptors. Finally, KEGG pathway enrichment analysis was performed on 35 differentially expressed genes to obtain a significantly

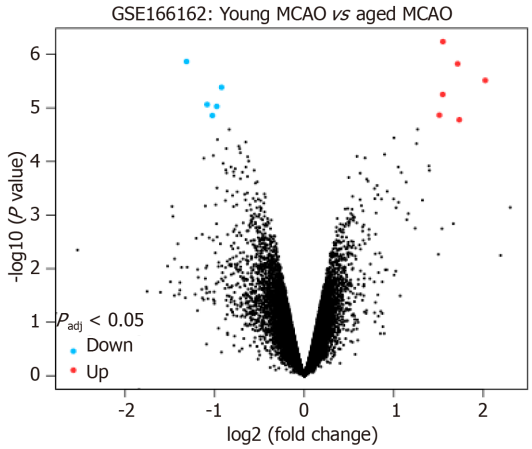

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Figure 2 Volcanic map of the GSE166162 chip dataset. Volcanic map could visually display red upregulated genes and blue downregulated genes. MCAO: Middle cerebral artery occlusion.

enriched pathway: The c-AMP signalling pathway. Studies have shown that the main target of c-AMP was the c-AMP-dependent protein kinase A and exchange protein directly activated by c-AMP. We might reduce the incidence of ischaemia in young rats by interfering with corresponding targets, thereby reducing their disability and mortality. The c-AMP signalling pathway can promote vascular endothelial repair and inhibit vascular intimal proliferation and platelet aggregation by regulating downstream effector molecules, thereby inhibiting vascular remodelling. In addition, activation of the c-AMP pathway can also alleviate ischaemic stroke-reperfusion injury, promote neuronal repair, and improve poststroke cognitive function[15,16]. The c-AMP signalling pathway may be a key pathway for the intervention of stroke-related diseases such as cerebral infarction and vascular cognitive impairment in young people and has extremely important clinical significance and research value.

To date, there have been no relevant research papers at home and abroad reporting the key signalling pathway involved in the development ischemic stroke in young rats. In this paper, we identified that the c-AMP signalling pathway is the key signalling pathway for young rats developing acute ischemic infarction through the methods of related gene analysis, which has extremely significant clinical significance. However, the subjects of this study are rats, and the sample size is relatively small. If more gene expression profile data are published in the future, further in-depth analysis could be conducted to verify the research results. Finally, we need to collect a certain number of clinical cases in the future to verify whether the research results are suitable for human beings, so as to realize the clinical transformation of major basic scientific discoveries.

CONCLUSION

Our study demonstrated that the c-AMP signalling pathway may be the key pathway in the intervention of cerebral infarction in young people. Further fundamental studies are needed to comprehensively explore the impact of the key pathway response on infarction in young people to finally achieve clinical transformation.

ARTICLE HIGHLIGHTS

Research background

The incidence rate of cerebral infarction in young people is increasing day by day, the age of onset tends to be younger, and its internal pathogenesis and mechanism are very complicated, which leads to greater difficulties in treatment. Therefore, it is essential to analyze the key pathway that affects the onset of cerebral infarction in young people from the perspective of genetics.

Research motivation

To compare the differentially expressed genes in the brain tissue of young and aged rats with middle cerebral artery occlusion and to analyse their effect on the key signalling pathway involved in the development of cerebral ischaemia in young rats.

Research objectives

To compare the differentially expressed genes in the brain tissue of young and aged rats with middle cerebral artery occlusion and to analyse their effect on the key signalling pathway involved in the development of cerebral ischaemia in young rats.

Research methods

The Gene Expression Omnibus 2R online analysis tool was used to analyse the differentially expressed genes in the GSE166162 dataset regarding the development of cerebral ischaemia in young and aged groups of rats. DAVID 6.8 software was further used to filter the differentially expressed genes. These genes were subjected to Gene Ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis to determine the key gene pathway that affects the occurrence of cerebral ischaemia in young rats.

Research results

Thirty-five differentially expressed genes (such as *Igf2*, *Col1a2*, and *Sfrp1*) were obtained; 73 GO enrichment analysis pathways are mainly involved in biological processes such as drug response, amino acid stimulation response, blood vessel development, various signalling pathways, and enzyme regulation. They are involved in molecular functions such as drug binding, protein binding, dopamine binding, metal ion binding, and dopamine neurotransmitter receptor activity. KEGG pathway enrichment analysis showed a significantly enriched pathway: The cyclic adenosine monophosphate (c-AMP) signalling pathway.

Research conclusions

The c-AMP signalling pathway might be the key pathway in the intervention of cerebral infarction in young people.

Research perspectives

Further fundamental studies are needed to comprehensively explore the impact of the key pathway response on infarction in young people to finally achieve clinical transformation.

FOOTNOTES

Author contributions: Xia Y and Zhu R designed the research and wrote the paper; Xia Y and Liu H performed the research; Liu H contributed new reagents; Xia Y analyzed the data.

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