*Pakistan J. Zool., pp 1-8, 2021.* **DOI**: https://dx.doi.org/10.17582/journal.pjz/20201105061129

# Relationship between Glucose Metabolism Abnormalities and Neuronal Autophagy and Apoptosis in Patients with Ischemic Stroke and Cognitive Impairment

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**Article Information**
**Received 05 November 2020**
**Revised 04 January 2021**
**Accepted 13 February 2021**
**Available online 08 October 2021**

**Authors' Contribution**
**YF collected the samples. XP analysed the data, conducted the experiments and analysed the results. Both authors discussed the results and wrote the manuscript.**

**Key words**
**Ischemic stroke, Glucose metabolism abnormalities, Neuronal autophagy and apoptosis, Cognitive function.**

## ABSTRACT

This study was aimed to investigate the relationship between glucose metabolism abnormalities and neuronal autophagy and apoptosis in patients with ischemic stroke and cognitive impairment. Glucose metabolism abnormalities and cognitive function in patients with ischemic stroke were detected by glucose tolerance test and neuropsychological test. Morris water maze test was used to detect learning and memory ability of MCAO model rats. RT-PCR and Western Blot method were used to detect the expression of autophagy and apoptosis genes in neurons. We found that patients with ischemic stroke suffered from different degrees of impaired glucose tolerance, and the HbA1c index of patients with impaired glucose regulation and diabetes was higher than that of the normal glycemic group at the beginning and 3 months after the onset. The proportion of LAA and SAO in the two groups, other than the normal blood glucose group, reached 61.90%, 52.00%, 33.30%, and 40.00%, respectively. Compared with the other two groups, the MMSE and Mattis dementia scale scores and their attention were different in the impaired glucose regulation group; animal experiments found that the learning ability and memory ability of rats with ischemic stroke were reduced, and the expression levels of neuron autophagy-related genes Bclin-1, LC3, Bcl2 and apoptosis-related genecapase 3 increased. To conclude, aggravated cognitive dysfunction in patients with ischemic stroke could cause glucose metabolism abnormalities and increase neuronal autophagy and apoptosis.



## INTRODUCTION

Stroke is the first major cause of disability and death in the world (Mazzoleni *et al*., 2019). Studies have pointed out that the probability of cognitive dysfunction in stroke patients is 9 times that in non-stroke patients. 54%-64% of patients with cerebrovascular diseases have cognitive dysfunction. One third of them may develop into dementia (Nielsen *et al*., 2017). Ischemic stroke is characterized by high mortality and high incidence, and its common disease is cognitive dysfunction. More and more people argue that glucose metabolism abnormalities in the brain will cause the loss of neurons in the body (Barros *et al*., 2018). There is a transitional stage between cognitive impairment and normal brain aging and dementia, which is mainly manifested as memory impairment. While patients with glucose metabolism abnormalities suffer from different degrees of cognitive dysfunction. The reasons for hyperglycemia in patients with ischemic stroke: on the one hand, a series of neuroendocrine abnormalities in the body under emergency conditions, such as stress hyperglycemia and glucose metabolism disorder, lead to the destruction of the original physiological environment; on the other hand, due to the deterioration of glucose metabolism abnormalities, when the patient has hyperglycemia, his/her blood-brain barrier is destroyed, which leads to hemorrhage transformation in the body and increases the risk of cerebral hemorrhage and thrombolysis (Cao *et al*., 2019).

Autophagy is a way of lysosomal-dependent degradation in eukaryotic cells, which is more obvious in injury and stress. In basic research, it has been proved that the occurrence of autophagy in stroke patients is related to the occurrence and development of cognitive impairment. At the same time, it has been confirmed that electroacupuncture has obvious curative effect on ischemia-reperfusion injury (Song *et al*., 2018). Under normal physiological conditions, patients' autophagy level is low, and its main function is to remove degraded proteins in cells. When stimulated by ischemia-reperfusion and other factors, the autophagy mechanism of the body is started to remove damaged mitochondria in the body and improve the tolerance to hypoxia, playing a certain protective role (Wang *et al*., 2018). It is found that when the body is in

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0030-9923/2021/0001-0001 $ 9.00/0

a state of ischemia and hypoxia, the death rate of nerve cells increases. At this time, the activation of autophagy significantly improved the cell survival rate of patients. Therefore, it is considered that autophagy in emergency state can play a role in protecting nerve cells and at the same time affect physiological and pathological obstacles of cells (Zhang *et al*., 2018). For example, intracellular calcium overload, inflammatory reaction, free radical damage and other factors lead to neurological dysfunction. Apoptosis is a form of cell death under physiological and pathological conditions, and its biochemical characteristic is mainly the oligonucleosome produced by endogenous endonuclease after cutting the nucleosome DNA chain (Lu *et al*., 2019). It is pointed out that apoptosis is related to the ischemic injury of the body and is the main way of neuronal death. It is believed that apoptosis is related to the severity and type of ischemia in patients. It is pointed out that ischemic brain tissue is prone to inflammatory reaction, is characterized by infiltration of peripheral leukocytes and activation of microglia. Activated microglia can trigger inflammatory reaction by releasing reactive oxygen species, cytokines, glutamate and protease, and then lead to the death of neurons in the body (Meurer *et al*., 2018). In this paper, the relationship between glucose metabolism abnormalities and neuronal autophagy and apoptosis in patients with ischemic stroke was studied, which is of great value for the treatment of patients with ischemic stroke and their prognosis and rehabilitation.

## MATERIALS AND METHODS

From June 2016 to July 2019, 132 patients diagnosed as ischemic stroke in Department of Neurology of Hangzhou People's Hospital were selected as experimental subjects. All experiments were carried out only after the subjects had signed the informed experimental consent. Inclusion criteria of our study included: Acute onset with high signs and symptoms for several hours; cerebral hemorrhage and other diseases were excluded by MRI or head CT; MRI or cranial CT found responsible infarct lesions; focal neurological impairment occurred, and a small part was comprehensive neurological impairment. all the selected patients were hospitalized within 3 days after onset. Before onset, the patients had normal body function and good adaptability, and could cooperate with the examination. They voluntarily joined neuropsychological examination.

Exclusion criteria of our study included: Complicated with coma, consciousness disorder; patients with cerebral infarction caused by valvular heart disease and atrial fibrillation were given anti-inflammatory drugs or glucocorticoids in large doses; there were cerebrovascular events in the past medical history or there were old cerebrovascular lesions in the brain; patients who were illiterate or whose previous medical history contained cognitive decline or who could not be tested for neuropsychology were excluded; patients with white matter degeneration and brain atrophy by imaging examination, and patients who had severe diseases of liver, heart, blood, kidney and other important organs and nervous system diseases, such as Parkinson's disease, brain trauma, brain tumor, other mental disorders such as depression and anxiety, or had a long history of alcohol and drug abuse.

*Patient classification and condition analysis*

After admission, patients were classified according to "TOAST" (mainly according to the American clinical characteristics of patients). They were classified and analyzed according to NIHSS issued by American Institutes of Health, and their severity was judged according to their scores, among which the score of 0-6 points was mild; the score of 7-15 points was moderate; and the score over 16 points was severe.

*Experimental animals*

Sixty SPF adult healthy male mice (SD) aged 35-45 days and weighing about 200±20g were purchased from Beijing Weitong Lihua with the license number SCXK (Jing) 2017-0014. All animals ate food and drank water freely, and were given alternate illumination for 12 h every day.

*Glucose tolerance test*

Oral glucose tolerance test was performed when the patient's condition was relatively stable, and blood glucose content, glycosylated hemoglobin, insulin and other indexes were detected at fasting state, 30 min and 120 min. The numerical calculation formula of insulin resistance HOMA-IR= fasting insulin X fasting blood glucose number / 22.5, and the patient's glucose disposal index = insulin proliferation number at 30 min/proliferation number of blood glucose concentration at the same time × 1 / insulin resistance index. At the same time, the diagnosis and classification criteria of metabolic abnormality and diabetes were based on WHO diabetes classification and diagnosis criteria.

*Neuropsychological test*

The Mzttis dementia scale and MMSE examination scale were used to test the patients' overall cognitive function, and their attention, memory, executive ability, information processing ability and visual space ability were tested. The test standards were in accordance with internationally recognized evaluation standards. The test

was independently completed by a trained professional neurologist in a quiet environment.

Criterion for judging the degree of cognitive dysfunction: MMSE scale: the score of middle school education and above fewer than 24 points, the score of primary school education fewer than 20 points, and the score of illiteracy fewer than 17 points are considered as cognition impairment. When the score is 13-23 points, it is mild cognition impairment; when the score is 5-12 points, it is moderate cognition impairment; when the score is <5 points, it is high cognition impairment.

*Preparation and evaluation of cerebral ischemia-reperfusion model*

Sixty mice were randomly divided into three groups: sham operation group, model group and lovastatin treatment group. The MCAO model was established for the model group and the lovastatin group by suture method, and the occlusiontime was 120min; in the sham operation group, only surgery was performed without occlusion.

Evaluation method: TTC staining was used to observe and calculate the area of cerebral infarction in mice.

*Test of cognitive dysfunction in mice with ischemic stroke*

Morris water maze method was used to evaluate the memory of mice in each group by the time spent in space exploration and the times of crossing the platform, and their learning ability was evaluated by the times of escaping the latent period.

*mRNA expression level of neuronalautophagy and apoptosis-related genes in mice*

After killing 5 mice in each group, their RNA was extracted from the hippocampus and transcribed into cDNA. The expression levels of their bcl-1, LC3, bcl-2 and apoptosis-related gene capase 3 were detected by RT-PCR.

*Western blot test*

After killing 5 mice in each group, their protein was extracted by adding tissue protein lysate, and was boiled and cooled for later use. SDS-page electrophoresis and PVDF membrane transfer methods were used to separate and transfer the protein. After antibody incubation, the protein expression levels of neuron autophagyand apoptosis-related genes in each protein group were analyzed by taking pictures under chemiluminescence imager.

*Statistical analysis*

SPSS 18.5 was used to analyze the data, and the data conforming to normal distribution was expressed as (±s), and variance analysis and T test were carried out. As for the test standard, $P > 0.05$ indicated that the data had no statistical significance.

## RESULTS

*Glucose metabolism in patients with ischemic stroke*

The results of oral glucose tolerance test in 132 patients with ischemic stroke are shown in Table I. It can be seen from Table I that 58 cases of 132 patients with ischemic stroke were in line with the diagnosis of diabetes: 46 cases were impaired glucose regulation, including 30 cases of impaired glucose tolerance, 4 cases of simple glucose tolerance, 12 cases of impaired fasting glucose and impaired glucose tolerance. 28 cases were normal glucose. Three months later, 50 patients were diagnosed as diabetes; 42 patients diagnosed as impaired glucose regulation, and 40 patients were diagnosed as normal blood glucose.

**Table I.- Types of glucose metabolism in patients with ischemic stroke.**

| Type | Cases at the initial stage (%) | Cases after 3 months (n/%) |
|---|---|---|
| Diabetes | 58(44.01) | 50 (37.80) |
| Simple impaired fasting blood glucose; impaired sugar regulation | 4 (3.31) | 42 (31.80) |
| Impaired glucose tolerance | 30 (24.86) | 0 (0) |
| Impaired glucose tolerance+ impaired fasting blood glucose | 12 (9.94) | 0 (0) |
| Normal blood glucose | 28 (21.20) | 40 (30.30) |

Table II showed related indexes of glucose metabolism in 132 patients. It can be seen that the HbA1c indexes of patients with impaired glucose regulation and diabetes are higher than those of patients with normal blood glucose at the initial stage and after 3 months, and there is no significant difference between the follow-up indexes of patients at the initial stage and after 3 months ($P$>0.05). Compared with the impaired glucose regulation group, the insulin resistance index in diabetes group has no statistical significance ($P > 0.05$), but statistical significance exists in all other groups ($P < 0.05$). At the same time, the DI index of each group was statistically significant ($P < 0.05$).

*Disease evaluation of patients with ischemic stroke*

The results of TOAST classification and disease score of patients in each group are shown in Table III. It can be seen from Table III that there is no difference in the proportion of each sub-type of stroke patients in the

glucose metabolism group ($P$ >0.05). But the common subtypes are LAA and SAO, among which the proportions of LAA in the two groups except the normal blood glucose group reached 61.90% and 52.00%, respectively, and the proportions of SAO reached 33.30% and 40.00%, respectively.

**Table II.- Glucose metabolism indices of patients with normal glucose, impaired glucose metabolism and diabetes.**

| Type of patients | HbA1c | HOMA-IR | DI |
|---|---|---|---|
| **Normal blood glucose group (28 cases)** | | | |
| Initial period | 5.71±0.52 | 2.37 (0.54-16.03) | 6.27 (0.90-51.04) |
| After 3 months | 5.63±0.41 | 2.53 (0.79-7.55) | 6.44 (1.85-77.44) |
| **Impaired glucose regulation group (46 cases)** | | | |
| Initial period | 6.41±1.00[a] | 3.96 (1.24-9.68) [a] | 1.84 (0.15-13.81) [a] |
| After 3 months | 6.23±0.96[a] | 3.62 (1.37-5.84) [a] | 0.75 (0.06-4.77) [a] |
| **Diabetes group (58 cases)** | | | |
| Initial period | 7.74±1.39[a] | 4.65 (0.71-24.86) [a] | 1.89 (0.24-24.67) [ab] |
| After 3 months | 7.32±1.21[ab] | 4.86 (1.63-19.23) [ab] | 0.66 (0.09-2.98) [ab] |

HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance.
[a], statistically significant difference compared with normal blood glucose group, $P < 0.05$. [b], statistically significant difference compared with the impaired glucose regulation group, $P < 0.05$.

**Table III.- Glucose metabolism of patients with ischemic stroke with different scores and types.**

| Type | Normal blood glucose group (%) | Impaired glucose regulation group (%) | Diabetes group (%) |
|---|---|---|---|
| **TOAST classification** | | | |
| SAO | 20 (50.00) | 14 (33.30) | 20 (40.00) |
| LAA | 14 (35.00) | 26 (61.90) | 26 (52.00) |
| CE | 4 (10.00) | 2 (4.80) | 4 (8.00) |
| SOE+SUE | 2 (5.00) | 0 (0.00) | 0 (0.00) |
| **NIHSS score of patients upon admission** | | | |
| 0-6 | 28 (70.00) | 28 (66.70) | 30 (60.00) |
| 7-15 | 4 (10.00) | 12 (28.60) | 18 (36.00) |
| ≥16 | 8 (20.00) | 2 (4.80) | 2 (4.00) |

LAA, atherosclerosis of aorta; CE, cardiogenic embolism; SAO, small artery occlusion; SOE, stroke of other etiology; SUE, stroke of unknown etiology. There was no statistical significance among the groups ($P>0.05$).

*Cognitive dysfunction of patients*

The scores of cognitive dysfunction of patients in different groups are shown in Table IV. It can be seen that compared with other two groups, the scores of MMSE scale and Mattis dementia scale and their attention in impaired glucose regulation group are statistically significant ($P$ <0.05).

*MCAO model evaluation*

TTC staining results are shown in Figure 1, and infarction area comparison is shown in Table V. The TTC staining results show that the experimental modeling was successful.

**Table IV.- Cognitive function scores of patients.**

| Type | Normal blood glucose group | Impaired glucose regulation group | Diabetes group | F value | P value |
|---|---|---|---|---|---|
| MMSE scale | 21.69±5.36[a] | 11.25±4.92 | 20.98±5.83[a] | 4.221 | 0.002 |
| Mattisscale | 102.63±21.94 | 66.74±20.39 | 101.59±23.10 | 3.198 | 0.014 |
| Attention | 15.32±4.06[a] | 8.00±3.07 | 14.74±4.75[a] | 3.586 | 0.007 |
| Immediate logical memory | 6.69±5.76 | 0 | 7.63±6.13 | 2.205 | 0.068 |
| Delayed logical memory | 5.17±5.88 | 0 | 4.75±5.52 | 1.826 | 0.124 |
| Delayed logical memory | 2.91±1.63 | 1.58±1.36 | 2.57±1.64 | 1.287 | 0.175 |
| Auditory memory after delaying 30 min | 0.92±0.12 | 0 | 0.55±1.17 | 1.376 | 0.243 |
| Rey visual memory | 3.27±2.35 | 0 | 1.33±3.31 | 1.821 | 0.124 |
| Stroop C executive function | 35.21±10.54 | 34.43±3.04 | 33.90±10.56 | 0.235 | 0.864 |
| Semantic fluency | 10.27±4.38 | 5.31±3.86 | 10.47±4.52 | 1.376 | 0.244 |
| Stroop A information processing ability | 46.53±10.76 | 49.57±1.13 | 46.30±10.84 | 0.202 | 0.863 |
| Rey picture visual spatial structure ability | 9.59±12.03 | 0.00±0.00 | 6.98±8.87 | 2.203 | 0.067 |
| Ability of visual spatial structure in clock drawing experiment | 14.30±7.98 | 7.50±8.64 | 14.31±9.04 | 2.004 | 0.093 |

Statistically significant difference compared with impaired glucose regulation group, $P < 0.05$.

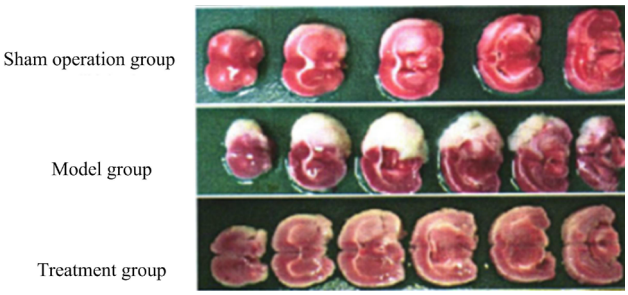


Fig. 1. TTC staining results of patients in each group.

**Table V.- Cerebral infarction area of experimental mice.**

| Group | n | Infarction area |
|---|---|---|
| Sham operation group | 20 | 0.00±0.00 |
| Stroke | 20 | 65.63±5.21 |
| Treatment group | 20 | 47.12±3.96 |
| *F* value | - | 58.976 |
| *P* value | - | 0.001 |

*Cognitive dysfunction of mice*

The test results of learning and memory ability of mice in each group are shown in Table VI. It can be seen from Table VI that compared with sham operation group, the learning ability and memory ability of mice in stroke group were decreased.

*Expression of neuron autophagy and apoptosis-related genes in mice*

The mRNA expression level of neuron autophagy and apoptosis-related genes in mice is shown in Table VII. Table VII which shows that compared with the sham operation group, the molecular expression levels of bcl-1, LC3, bcl-2 and apoptosis-related gene capase 3 in stroke group all increased. The Agarose gel electrophoresis is shown as Figure 2.

Table VIII shows that protein expression levels of neuron autophagyand apoptosis-related genes of mice. The protein expression levels of bcl-1, LC3, bcl-2 and apoptosis-related gene capase 3 in stroke group all increased compared with sham operation group (Fig. 3).

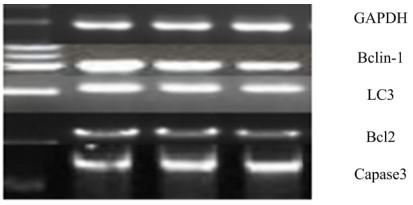


Fig. 2. The Agarose gel electrophoresis results of expression level of neuron autophagy and apoptosis related gene in mice.

**Table VI.- Comparison of learning and memory ability of experimental mice in each group.**

| Group | Escaping the latent period | Time of space exploration | Times of crossing the platform |
|---|---|---|---|
| Sham operation group | 20.53±1.02 | 45.93±4.52 | 8.32±1.03 |
| Stroke | 36.68±5.31 | 22.13±3.11 | 2.74±0.98 |
| Treatment group | 30.15±2.17 | 32.19±2.13 | 4.68±1.01 |
| *F* value | 61.225 | 58.372 | 63.892 |
| *P* value | 0.001 | 0.001 | 0.001 |

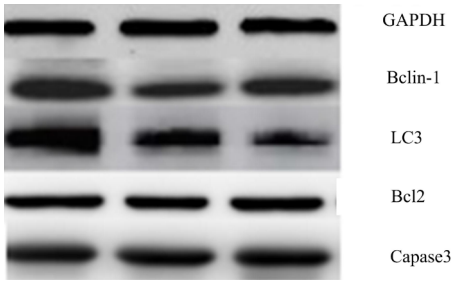


Fig. 3. The Agarose gel electrophoresis results of expression levels of bcl-1, LC3, bcl-2.

**Table VII.- Expression level of neuron autophagy and apoptosis-related genes of experimental mice in each group.**

| Group | Bclin-1/GAPDH | LC3/GAPDH | Bcl2/GAPDH | Capase 3/GAPDH |
|---|---|---|---|---|
| Sham operation group | 0.94±0.05 | 0.72±0.06 | 0.62±0.01 | 0.76±0.02 |
| Stroke | 2.08±0.21[ab] | 2.00±0.24[ab] | 4.32±0.98[ab] | 3.65±0.16[ab] |
| Treatment group | 1.55±0.09[a] | 1.57±0.03[a] | 2.14±0.38[a] | 1.65±0.21[a] |
| *F* value | 15.203 | 12.365 | 16.320 | 19.701 |
| *P* value | 0.010 | 0.008 | 0.005 | 0.006 |

[a], statistically significant difference compared with sham operation group, $P<0.05$. [b], statistically significant difference compared with stroke group, $P<0.05$.

**Table VIII.- Protein expression levels of neuron autophagy and apoptosis-related genes of experimental mice in each group.**

| Group | Bclin-1/GAPDH | LC3/GAPDH | Bcl2/GAPDH | Capase 3/GAPDH |
|---|---|---|---|---|
| Sham operation group | 2.96±1.02 | 5.34±1.24 | 1.29±0.65 | 1.00±0.01 |
| Stroke | 6.35±5.31[ab] | 10.28±2.15[ab] | 4.11±0.21[ab] | 4.02±1.01[ab] |
| Treatment group | 4.21±2.17[a] | 8.09±1.27[a] | 3.01±0.02[a] | 2.32±0.17[a] |
| *F* value | 16.820 | 22.692 | 12.397 | 16.552 |
| *P* value | 0.006 | 0.001 | 0.005 | 0.001 |

[a], statistically significant difference compared with sham operation group $P < 0.05$. [b], Statistically significant difference compared with stroke group, $P<0.05$.

## DISCUSSION

Ischemic stroke is a general term for diseases with different severity, different clinical outcomes and different etiology. The main factors that determine the severity of the disease include the range and location of infarct focus, the size of occluded blood vessels, and the degree of brain injury caused by intracranial hypertension and secondary brain edema (Meurer *et al*., 2018). Cognitive dysfunction has a serious impact on patients' social and family life and living quality. Therefore, screening the cognitive function of patients with ischemic stroke and exploring the mechanism of action are effective ways to improve the prognosis of stroke patients.

In this study, it was found that patients with ischemic stroke had different degrees of cognitive dysfunction when their glucose metabolism was abnormal. Meanwhile, the learning and memory abilities of mice with ischemic stroke were decreased, and the autophagy-related genes bcl-1, LC3, bcl-2 and apoptosis-related gene capase 3 were up-regulated.

Glucose metabolism abnormalities will increase the risk of cognitive impairment of patients (Ploran *et al*., 2019). Viswanathan *et al*. (2019) found that the incidence of Alzheimer's disease in patients with type 2 diabetes is significantly higher than that in patients with normal glucose metabolism abnormalities, and the risk ratio is as high as 25%. However, the cognitive impairment of patients with type 2 diabetes is characterized by the decrease of processing speed and language ability. And with the increase of age, the impaired area of cognitive function will extend to other areas. Dolo *et al*. (2018) found that after half a year's aerobic exercise, the insulin sensitivity of patients can be significantly improved. In addition, the executive ability of patients can be enhanced, and the expression level of Aβ42 can be reduced. The research on cardiovascular patients shows that when patients have glucose metabolism abnormalities, their MMSE score is 0.4 lower than that of normal patients. With the increase of blood glucose concentration, the branches decrease continuously, and there is a negative correlation between them (Oliveira *et al*., 2018). In the MMSE test of 182 elderly people, it was found that the MMSE score of 3% patients with impaired fasting glucose tolerance was greater than 28.3, and the probability ratio of cognitive impairment of the patients reached 9.08 (Dubois *et al*., 2018). Studies have pointed out that there is a negative correlation between glucose metabolism abnormalities in local brain tissue and insulin resistance. When glucose metabolism abnormalities occur, insulin resistance can be used as an effective index to prevent cardiovascular diseases when the abnormalities are improved (Fallah *et al*., 2018).

It is found that the regulatory mechanism of autophagy network after ischemia-reperfusion injury mainly depends on the P13K signaling pathway, the expression level changes of apoptosis-related genes P53 and Bcl-2, and the intracellular calcium concentration. Surinkaew *et al*. (2018) found that Vps34 can directly induce autophagy in body cells under hypoxia. According to reports, the inflammatory response regulated by NF-kB signal is related to autophagy. For example, HIF-1 can induce transcription and expression of many downstream genes (Jian *et al*., 2019). Cerebral ischemia can enhance the expression of HIF-1α in microglia, and initiate autophagy function through Beclin1 pathway. It induces cell death and verifies the effect to further aggravate the neurological damage of patients (Shang at al., 2017). In the model study of mice with cerebral ischemia, it is found that the activity of lysosomes and autophagy of neurons around the ischemic tissue is obviously enhanced, and it is considered that autophagy activity of the body has a protective effect on the ischemic area (Lu *et al*., 2019). In the hypoxic-ischemic mice model, the expression level of autophagy-related gene Beclin-1 in cerebral cortex neurons and hippocampus increased and reached its peak within 24 h.

However, the expression level of autophagy-related gene Beclin-1 in mice added with autophagy inhibitor before ischemia was significantly down-regulated. The process of apoptosis is mainly regulated by BCL family and caspase family, in which BCL-xl and caspase-3 are the inhibition genes of apoptosis and the key genes of signal transduction in apoptosis process, respectively. And the activation of caspase-3 is the key to realize apoptosis, and it is also the promoter of neuronal apoptosis. When Chrelin is injected into the lateral ventricle of diabetic rats, the expression of BCL-xl can be increased and the expression of caspase-3 can be decreased, which can inhibit the apoptosis of hippocampal neurons in brain tissue and improve the cognitive dysfunction.

## CONCLUSION

Glucose metabolism abnormalities and increased neuronal autophagy and apoptosis in patients with ischemic stroke could reduce their cognitive function.

*Statement of conflict of interest*

The authors have declared no conflict of interests.

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