ClinicSearch

Clinical Research and Clinical Reports

Elizaveta I. Bon *

Open Access

Research Article

Comparative Characteristics of The Pool of Amino Acids in Partial Cerebral Ischemia and Subtotal cerebral Ischemia in Outbred White Rats

Bon E. I *, Maksimovich N. Ye, Doroshenko Ye.M, Smirnov V.Yu, Razvodovsky Yu.Ye, Portonenko A.M., Holik S.V

[1]Grodno State Medical University, Grodno, Belarus

Correspondence Author: Elizaveta I. Bon, Grodno State Medical University, Grodno, Belarus

Received Date: April 12, 2023 **Accepted Date**: April 19, 2023 **Published Date**: April 28, 2023.

Citation: Elizaveta I. Bon, Maksimovich N.Ye., Doroshenko Ye.M., Smirnov V.Yu., Razvodovsky Yu.Ye., et all (2023), Comparative Characteristics of The Pool of Amino Acids in Partial Cerebral Ischemia and Subtotal Cerebral Ischemia in Outbred White Rats, *Clinical Research and Clinical Reports*, 2(2); **DOI:**10.31579/2835-8325/015

Abstract

Cerebrovascular diseases are widespread throughout the world. In these diseases, the pool of amino acids in the brain changes. One-hour SCI is characterized by the following changes in the AAs pool: a decrease in the content of sulfur-containing AAs, with a decrease, in contrast to SCI, of both methionine and cysteate, as a reflection of a higher activity of oxidative stress in SCI. Along with this, in subtotal cerebral ischemia, as in PCI, an increase in the content of L-arginine, a tendency to an increase in the content of the inhibitory neurotransmitter glycine, and a decrease in aspartate and glutamate as AAs with the properties of excitatory neurotransmitters, as well as tryptophan, valine and leucine, were noted. At the same time, in contrast to PCI, there was no increase in the level of glutamate and a decrease in the levels of BCAAs. Studies of the pool of amino acids in PCI and SCI will serve as a fundamental basis for the development of methods for diagnosing and correcting cerebrovascular pathology.

Keywords: pool of amino acids; ischemia; rat; experimental brain

Introduction

Cerebrovascular diseases are widespread throughout the world. In these diseases, the pool of amino acids in the brain changes. Studies of the pool of amino acids in PCI and SCI will serve as a fundamental basis for the development of methods for diagnosing and correcting cerebrovascular pathology [1,2,11].

Materials and methods of research

The experiments were carried out on 72 male outbred white rats weighing 260±20 g in compliance with the requirements of the Directive of the European Parliament and of the Council No. 2010/63/EU of September 22, 2010 on the protection of animals used for scientific purposes.

Partial cerebral ischemia (PCI) modeling was carried out under conditions of intravenous thiopental anesthesia (40-50 mg/kg). PCI was modeled by ligation of one CCA on the right.
Subtotal cerebral ischemia (SCI) was modeled by simultaneous ligation of both common carotid arteries (CCA).
The material was taken 1 hour after the operation. The control group consisted of sham-operated rats of the same sex and weight.

Method for studying the pool of amino acids in the brain

After extraction of the brain, a fragment of the parietal cortex and hippocampus was taken, followed by freezing in liquid nitrogen.

Sample preparation for the study included homogenization in a 10-fold volume of 0.2 M perchloric acid, centrifugation for 15 min at 13,000 g at 4°C, followed by collection of the supernatant. Amino acids were analyzed by reversed-phase chromatography with pre-column derivatization with o-phthalaldehyde and 3-mercaptopropionic acid in Na-borate buffer on an Agilent 1100 chromatograph.

To prevent a systematic measurement error, brain samples from the compared control and experimental groups of animals were studied under the same conditions.

As a result of the research, quantitative continuous data were obtained. Since the experiment used small samples that had a non-normal distribution, the analysis was performed by nonparametric statistics using the licensed computer program Statistica 10.0 for Windows (StatSoft, Inc., USA). The data are presented as Me (LQ; UQ), where Me is the median, LQ is the value of the lower quartile; UQ is the value of the upper quartile. Differences between groups were considered significant at $p<0.05$ (nonparametric Games-Howell test).

Characterization of changes in the pool of amino acids in the brain of rats with partial cerebral ischemia

As shown earlier, when modeling partial cerebral ischemia (PCI) by unilateral ligation of the common carotid artery (CCA), after 1 hour, there were no pronounced morphological changes at the microscopic and ultrastructural levels. At the same time, no pronounced changes in the parameters of respiration of the mitochondrial fraction and changes in the parameters of the prooxidant-antioxidant balance[1-6,11] of brain homogenates, compared with the control, were observed, which reflects the relative safety of the enzymatic complexes of the electron transport chain in this model of ischemia. However, the results of behavioral tests indicated the development of a minor neurological deficit, and the existing decrease in the content of ATP synthase is the rationale for a possible cause of its development[1-6,11,12,17].

When studying the content of amino acids (AA) in brain homogenates in rats with one-hour PCI, an increase in the median values of the content of AA with neurotransmitter properties - glutamate by 20% in the parietal lobe (PL), $p<0.05$ and by 19% - in the hippocampus (Gp), $p<0.05$. An increase in glutamate levels while maintaining glutamine and GABA levels may be associated with an increase in glutaminase activity and/or transamination/reductive amination in neurons[1,2,13,23]. At the same time, changes in the levels of AA with the properties of excitatory neurotransmitters (aspartate and glutamate) had a multidirectional character: a tendency to an increase in the level of glutamate and to a decrease in aspartate. The decrease in aspartate, in contrast to glutamate, can be explained by its increased utilization as a glycogenic AA in oxidation reactions with the formation of energy[1-6,11,12,23-24].

As for the inhibitory mediators (GABA, glycine, taurine), one can note a trend towards an increase in their content: glycine - by 13% in PL ($p>0.05$), taurine - by 13% in PL ($p>0.05$) and by 29% - in Hp ($p>0.05$), GABA - by 14% in PL ($p>0.05$) and by 41% - in Hp ($p>0.05$) [18].

At the same time, the median level of GABA differed from its value in the control group in approximately the same way as that of glutamate, but the differences in their values were not statistically significant ($p>0.05$) [8,16,21].

Changes in the level of glycogenic AA (aspartate, asparagine, threonine, serine, glutamine, glutamate, glycine, alanine, valine, methionine, histidine, arginine) and ketogenic AA (leucine, lysine) for the brain, from the point of view of biochemical research, are mostly non-specific, since the processes of gluconeogenesis and ketogenesis do not occur in the brain. However, it should be noted that aspartate, glutamate and glycine play the role of neurotransmitters [10,12]; methionine is a precursor to a number of compounds with antioxidant properties; arginine is a substrate for NO synthase [1-6,14], and lysine is a precursor of the endogenous NMDA receptor antagonist α-aminoadipate [20,21].

n PCI, there was an increase in the median value.

L-arginine by 38% in PL ($p<0.05$) and by 46% in Hp ($p<0.05$). An increase in the content of L-arginine and citrulline in both studied brain structures indicate a decrease in the utilization of the substrate for NO synthase, which may be the cause of the existing slight neurological deficit due to the lack of NO, one of the mediators of the central nervous system that mediates the regulation of many processes, including higher nervous activity [14].

Also in the PL, a decrease in the median value of the methionine [15] content by 24% ($p<0.05$) was noted. At the same time, there was a tendency to an increase in the median values of the levels of other sulfur-containing AAs, to the greatest extent taurine by 29% - in Hp ($p> 0.05$), without changing it in PL, and cysteine sulfinic acid by 52% - in PL ($p> 0.05$) and by 29% in Hp ($p>0.05$), without changing the levels of cysteate and cystathionine, as a reflection of the low activity of oxidative processes in this type of cerebral ischemia[1-5,9,11,17].

In rats with PCI, there was a decrease in the median values of the content of branched hydrocarbon amino acids (BCAAs), as AAs, included in energy processes: valine - by 30% in PL ($p<0.05$) and by 37% - in Hp ($p< 0.05$), isoleucine - by 33% in PL ($p<0.05$) and 36% - in Hp ($p<0.05$) and leucine - by 30% in PL ($p<0.05$) and 32% - in Hp ($p<0.05$), which may be due to their utilization in transamination reactions [16].

Along with changes in BCAAs, in the studied parts of the brain, there was a tendency to a decrease in the levels of aromatic AAs (tyrosine, tryptophan, phenylalanine), which may reflect their utilization in the reactions of catecholamine and serotonin synthesis or a decrease in transport to the brain [16].

At the same time, in both studied departments there was a tendency to reduce the ratio of BCAAs to aromatic AAs from 1.43 to 1.06 in PL ($p>0.05$) and from 1.56 to 1.13– in Hp ($p>0.05$).

There was a decrease in the median values of all essential AAs (methionine by 24% in PL ($p<0.05$), valine by 30% in PL ($p<0.05$) and by 37% in Hp ($p<0.05$), isoleucine - by 33% in PL ($p<0.05$) and 36% - in Hp ($p<0.05$) and leucine - by 30% in PL ($p<0.05$) and 32% - in Hp ($p<0.05$), and there was also a tendency to a decrease in lysine by 55% - in PL and Hp ($p>0.05$) and threonine - by 32% ($p>0.05$) in both studied departments of the brain brain, which indicates their possible inclusion in metabolic processes, primarily as alternative energy substrates, as a result of inhibition of glucose utilization processes[1-7].

At the same time, the “Replaceable/Indispensable” ratio of AAs in the PCI group increased from 10.0 to 17.6 in PL ($p>0.05$) and from 8.4 to 16.4 in Hp ($p>0.05$), which may be a consequence of impaired utilization of essential AAs in protein synthesis reactions along with increased utilization of essential AAs.

So, one-hour PCI is characterized by the following changes in the AAs pool: an increase in glutamate and GABA without changing the ratio of excitatory and inhibitory amino acid transmitters, a decrease in the level of essential AAs with an increase in the "Essential/Essential" AAs ratio, as a reflection of increased utilization of essential AAs.

There were no changes in sulfur-containing AAs, except for a decrease in the content of methionine in the parietal lobe, which indicates minor violations of the prooxidant-oxidant balance in this model of CI [21]. There was a decrease in the content of amino acids with a branched hydrocarbon chain and a trend towards a decrease in the level of aromatic AAs (tyrosine, tryptophan, phenylalanine), with a decrease in their ratio, as a reflection of a more pronounced utilization of BCAAs, compared with aromatic AAs.

Changes in the pool of amino acids in the parietal lobe and hippocampus were of a similar nature, with the exception of a more significant decrease in the level of methionine in the parietal lobe, as a reflection of a higher activity of oxidative processes in this area of the brain [21].

Characteristics of changes in the amino acid pool of the cerebral hemispheres of rats with subtotal cerebral ischemia

Previous morphological studies in rats in the dynamics of subtotal cerebral ischemia (SCI) revealed a decrease in the size of neuronal perikarya, an aggravation of their elongation, a decrease in the number of normochromic and hyperchromic neurons, and an increase in the proportion of hyperchromic shriveled neurons and cells with pericellular edema [8,17,23]. At the ultrastructural level, with SCI, mitochondria swelled with a decrease in the number and length of their cristae, vacuolization of the granular endoplasmic reticulum was noted, and the predominance of free ribosomes over bound ribosomes. These morphological changes were the result of pronounced disturbances in energy metabolism, especially when succinate was used as a substrate in in vitro studies, indicating the most severe damage to the succinate dehydrogenase complex of the electron transport chain and was accompanied by a decrease in the content of ATP synthase, the enzyme responsible for the formation of ATP from ADP. Disturbances in the prooxidant-antioxidant balance in rats with SCI - a decrease in the total SH-groups of proteins and glutathione, the concentration of reduced glutathione, and an increase in the content of products that react with thiobarbituric acid, reflected a high activity of oxidative stress [2,3,17]. When modeling partial cerebral ischemia (PCI) by unilateral ligation of the common carotid artery (CCA), after 1 hour, there were no pronounced morphological changes at the microscopic and ultrastructural levels. Also, there were no pronounced changes in the respiratory parameters of the mitochondrial fraction with a slight decrease in the content of ATP synthase, which reflects the relative

safety of the enzymatic complexes of the electron transport chain in this model of ischemia and changes in the parameters of the prooxidant-antioxidant balance of brain homogenates[2,3,17,21].

Changes in the pool of amino acids (AA) in rats with SCI were as follows.

Compared with the indicators in the control group, in rats with SCI with an ischemic period of 1 hour in the parietal lobe, there was a decrease in the content of sulfur-containing amino acids: methionine by 12% ($p<0.05$) and cysteate by 28% ($p<0.05$), apparently as a result of the activation of oxidative stress [2,3]. In turn, a decrease in the level of cysteate prevents the synthesis of taurine, AA with mediator and antioxidant properties, but the level of the latter did not decrease, possibly due to its long half-life in the brain [21].

With PCI in PL, a decrease in the median value of the methionine content by 24% ($p<0.05$) was also noted, without changing the levels of cysteate and cystathionine, as a reflection of the low activity of oxidative processes in this type of cerebral ischemia [2,3,22].

The drop in the level of cysteate in PL in SCI, which wasn't observed in PCI, didn't lead to significant shifts in the levels of cysteine sulfinate, hypotaurine, and taurine, as noted above, which, along with a decrease in the level of methionine, may reflect a decrease in the flow of sulfur-containing amino acids along the cysteine dioxygenase pathway [2,23,24].

The revealed changes in the content of sulfur-containing AAs (decrease in the content of cysteate and methionine) in SCI are a reflection of the greater activity of oxidative processes compared to PCI [2,3,17,21].

Along with this, as in PCI, in rats with SCI, there was an increase in the level of the NO-synthase substrate L-arginine in PL by 28% ($p<0.05$), and in Hp by 35% ($p>0.05$). An increase in the level of L-arginine in SCI may be associated with a low activity of its utilization reactions due to oxygen deficiency, among which the formation of nitrogen monoxide (NO) plays a significant role. However, the level of the product of this reaction, ornithine, didn't change [14].

After 1 hour, as in the case of PCI, in subtotal cerebral ischemia(SCI), there was a tendency to increase the content of the inhibitory neurotransmitter glycine in both studied departments, while changes in the level of AAs with the properties of excitatory neurotransmitters (aspartate and glutamate)[7-9], on the contrary, tended to decrease, in contrast to PCI, where there was an increase in glutamate by 20% in the parietal lobe, $p<0.05$ and by 19% in the hippocampus (Hp), $p<0.05$.

With SCI in PL, there was a tendency to a decrease in the level of aromatic AA tryptophan (a source of serotonin), while changes in the content of other aromatic AAs (tyrosine, phenylalanine) in both PL and Hp, in contrast to PCI, were not observed ($p>0$, 05). This may be the result of increased serotonin synthesis or reduced transport to the brain. In this regard, we can assume a violation of the formation of catecholamines in SCI. In PCI, however, there was a tendency to a decrease in the levels of all aromatic AAs - tyrosine, tryptophan and phenylalanine ($p>0.05$).
Among the group of branched hydrocarbon amino acids (BCAAs), there was a tendency to decrease in valine by 21% in PL ($p>0.05$) and by 30% in Hp ($p>0.05$), while in rats with PCI showed a more significant decrease in the content of BCAAs, as AAs included in energy processes: valine - by 30% in PL ($p<0.05$) and by 37% - in Hp ($p<0.05$), isoleucine - by 33% in PL ($p<0.05$) and by 36% in Hp ($p<0.05$) and leucine - by 30% in PL ($p<0.05$) and by 32% in Hp ($p<0$, 05), which may be associated with their utilization as alternative energy sources. The absence of a pronounced decrease in the AAs of the BCAAs group with SCI is consistent with a significant decrease in energy processes with SCI [16].

As a result of changes in the levels of BCAAs and aromatic AAs, the coefficient of the ratio of the sum of BCAAs levels to the sum of aromatic AAs levels in SCI in PL didn't change ($p>0.05$), in contrast to Hp, where there was a tendency to decrease from 1.6 to 1 .2 ($p>0.05$), while in both studied departments there was a tendency for this indicator to decrease from 1.4 to 1.1 in PL ($p>0.05$) and from 1.6 to 1.1– in Hp ($p>0.05$).

Among the essential AAs in rats with SCI lasting 1 hour, there was a tendency to decrease in valine - by 21% in PL ($p>0.05$) and by 30% - in Hp ($p>0.05$), isoleucine - by 20% in Hp ($p>0.05$), leucine - by 17% in Hp ($p>0.05$), methionine - by 11% in PL ($p>0.05$) and by 18% - in HP ($p>0.05$), lysine - by 30% in SD ($p>0.05$) and by 41% - in Hp ($p>0.05$), threonine - by 24% in PL ($p>0.05$) and by 40% - in Hp ($p>0.05$), tryptophan - by 22% in PL ($p>0.05$) and by 24% - in Hp ($p>0.05$). At the same time, a significant decrease in all essential AAs was observed in PCI (valine - by 30% in PL ($p<0.05$) and by 37% in Hp ($p<0.05$), isoleucine - by 33% in PL ($p<0.05$) and by 36% in Hp ($p<0.05$) and leucine - by 30% in PL ($p<0.05$) and by 32% in Hp ($p<0.05$), methionine by 24% - in PL ($p<0.05$), and there was also a tendency to reduce lysine by 55% - in PL and Hp ($p>0.05$) and threonine - by 32% ($p>0.05$) in both studied parts of the brain, which indicates their possible more active involvement in metabolic processes than in SCI, primarily as alternative energy substrates due to inhibition of glucose utilization processes.

At the same time, the indicator of the "Replaceable / Essential" AAs ratio in the SCI group increased from 10.0 to 13.1 ($p> 0.05$) in PL ($p> 0.05$) and from 8.4 to 11.9 in Hp ($p>0.05$), which may be a consequence of impaired utilization of essential AAs in protein synthesis reactions along with increased utilization of essential AAs. With PCI, the indicator of the "Replaceable / Indispensable" ratio of AAs increased to a greater extent: from 10.0 to 17.6 ($p> 0.05$) - in PL ($p> 0.05$) and from 8.4 to 16.4 – in Hp ($p>0.05$).

Conclusion:

Thus, one-hour SCI is characterized by the following changes in the AAs pool: a decrease in the content of sulfur-containing AAs, with a decrease, in contrast to SCI, of both methionine and cysteate, as a reflection of a higher activity of oxidative stress in SCI. Along with this, in subtotal cerebral ischemia, as in PCI, an increase in the content of L-arginine, a tendency to an increase in the content of the inhibitory neurotransmitter glycine, and a decrease in aspartate and glutamate as AAs with the properties of excitatory neurotransmitters, as well as tryptophan, valine and leucine, were noted. At the same time, in contrast to PCI, there was no increase in the level of glutamate and a decrease in the levels of BCAAs.

References

1. Bon, E. I. Disorders of Energy Metabolism in Neurons of the Cerebral Cortex During Cerebral Ischemia / E. I. Bon, N. Ye. Maksimovich, S.M. Karnyushko, S. M. Zimatkin, M.A. Lychkovskaya // Biomedical Journal of Scientific & Technical Research, 40:31932-31937.
2. 2.Bon, E. I. (2022). Severity of Oxidative Stress in Stepwise Cerebral Ischemia / E. I. Bon, N. Ye. Maksimovich, I.K. Dremza, N.V. Kokhan, I.N. Burak // Advance In Medical and Clinical Research,1-3.
3. Bon, E.I. (2022). Characteristics of disorders of the prooxidant-oxidant balance in rats with cerebral ischemia / E.I. Bon, N.E. Maksimovich, I.K. Dremza, M.A. Nosovich, K.A. Khrapovitskaya // Ulyanovsk biomedical journal, 3:97-106.
4. Bon, E.I. (2021). Experimental Cerebral Ischemia Causes Disturbances in Mitochondrial Respiration of Neurons / E. I. Bon, N. Ye. Maksimovich, I.K. Dremza, M.A. Lychkovskaya // Biomedical Journal of Scientific & Technical Research, 40: 32387-32392.
5. Bon, E.I. (2022). Respiration of mitochondria of brain neurons in rats with cerebral ischemia of varying severity / E.I. Bon, N.E. Maksimovich, I.K. Dremza, M.A. Nosovich, K.A. Khrapovitskaya // Ulyanovsk biomedical journal, 2:128-138.
6. Chandel NS. (2021). Amino Acid Metabolism. Cold Spring Harb Perspect Biol, 13(4): 040584.
7. Erecińska M, Nelson D, Wilson DF, Silver IA. (1984). Neurotransmitter amino acids in the CNS. I. Regional changes in amino acid levels in rat brain during ischemia and reperfusion. Brain Res,18:304(1):9-22.

8. Fabian Büttner, Christian Cordes, Frank Gerlach, Axel Heimann, Beat Alessandri, Ulrich Luxemburger, Ozlem Türeci, Thomas Hankeln, Oliver Kempski, Thorsten Burmester. (2009). Genomic response of the rat brain to global ischemia and reperfusion. Brain Research. 2009; 1252: 1-14.
9. Guo M.F., Yu J.Z., Ma C.G. (2011). Mechanisms related to neuron injury and death in cerebral hypoxic ischaemia. Folia Neuropathol. 49 (2): 78-87.
10. H. Shimizu, S.H. Graham, L.-H. (1993). Chang, J. Mintorovitch, T.L. James, A.I. Faden, P.R. Weinstein, Relationship between extracellular neurotransmitter amino acids and energy metabolism during cerebral ischemia in rats monitored by microdialysis and in vivo magnetic resonance spectroscopy, Brain Research, Pages 33-42.
11. Kieser DC, Cawley DT, Fujishiro T, Roscop C, Boissiere L, Obeid I, Gille O, Vital JM, Pointillart V. (2019). Cerebral ischaemia following anterior upper thoracic spinal surgery utilizing a partial manubrial resection. Eur Spine J, 28(3):463-469.
12. Luk'yanova L.D., Dudchenko A.M. (2007). Regulyatornaya rol' mitokhondrial'noy disfunktsii pri gipoksii i ee vzaimodeystvie s transkriptsionnoy aktivnost'yu [Regulatory role of mitochondrial dysfunction under hypoxia and its interaction with transcriptional activity]. Vestnik RAMN, 2: 3-13.
13. Maksimovich, N. E. (2020). The rat brain and its response to ischemia: monograph / N. E. Maksimovich, E. I. Bon, S. M. Zimatkin. - Grodno: GrGMU, 240.
14. Mammedova JT, Sokolov AV, Freidlin IS, Starikova EA. (2021). The Mechanisms of L-Arginine Metabolism Disorder in Endothelial Cells. Biochemistry (Mosc). 86(2):146-155.
15. Martínez Y, Li X, Liu G, Bin P, Yan W, Más D, Valdivié M, Hu CA, Ren W, Yin Y. (2017). The role of methionine on metabolism, oxidative stress, and diseases. Amino Acids, 49(12):2091-2098.
16. Nie C, He T, Zhang W, Zhang G, Ma X. (2018). Branched Chain Amino Acids: Beyond Nutrition Metabolism. Int J Mol Sci. 23;19(4):954.
17. Ramon Rodrigo, Rodrigo Fernandez-Gajardo, Rodrigo Gutiérrez, Jose Manuel Matamala, Rodrigo Carrasco, Andres Miranda-Merchak, Walter Feuerhake. (2013). Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. CNS Neurol Disord Drug Targets. 12 (5): 698-714.
18. Razak MA, Begum PS, Viswanath B, Rajagopal S. (2017). Multifarious Beneficial Effect of Nonessential Amino Acid, Glycine: A Review. Oxid Med Cell Longev,1716701.
19. Razvodovsky Yu.E. (2019). Influence of blockade of nitrogen monoxide synthesis by N-nitro-L-arginine methyl ester (L-NAME) on the content of free amino acids and biogenic amines in the cerebral cortex of rats with subtotal cerebral ischemia / Yu. E. Razvodovsky, V. Yu. Smirnov, E M. Doroshenko, N. E. Maksimovich, I. N. Semenenya // Bulletin of the National Academy of Sciences of Belarus. Gray medical sciences, 16:3.291-297.
20. Razvodovsky Yu.E. (2019). The content of amino acids and their derivatives in the cerebral cortex of rats with its partial ischemia / Yu. E. Razvodovsky, V. Yu. Smirnov, E. M. Doroshenko, N. E. Maksimovich, V.A. Pereverzev // Bulletin of the Smolensk State Medical Academy, 18:1:5-9.
21. Réus G.Z. (2022). Relationship of Oxidative Stress as a Link between Diabetes Mellitus and Major Depressive Disorder.
22. Slivka AP, Murphy EJ. (2001). High-dose methylprednisolone treatment in experimental focal cerebral ischemia. Exp Neurol, 167(1):166-172.
23. Takeda H, Yamaguchi T, Yano H, Tanaka J. (2021). Microglial metabolic disturbances and neuroinflammation in cerebral infarction. J Pharmacol Sci, 145(1):130-139.
24. Tan XL, Xue YQ, Ma T, Wang X, Li JJ, Lan L, Malik KU, McDonald MP, Dopico AM, Liao FF. (2015). Partial eNOS deficiency causes spontaneous thrombotic cerebral infarction, amyloid angiopathy and cognitive impairment. Mol Neurodegener. 24:10:24.