AUCTORES
Globalize your Research

Psychology and Mental Health Care

Özcan Özdemi *

Open Access

Review Article

Brain Hypoxia - Methodological Approaches to Experimental Modeling

Maksimovich N. Ye, Bon E.I.

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

***Corresponding Author**: Elizaveta I Bon, Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

Received date: May 22, 2024; Accepted date: June 06, 2024; Published date: June 14, 2024

Citation: Maksimovich N.Ye., Bon E.I, (2024), Brain Hypoxia - Methodological Approaches to Experimental Modeling, *Psychology and Mental Health Care*, 8(6): **DOI**:10.31579/2637-8892/281

Abstract

Appropriate models of cerebral pathology contribute to detailed representations of the pathogenesis of these disorders and, in addition, allow assessing the development of damage and adaptive mechanisms of the brain, which serves as a fundamental basis for improving the methods of their diagnosis, treatment, and prevention.

Keywords: brain, hypoxia; methodological approaches; experimental modeling

Introduction

Appropriate models of cerebral pathology contribute to detailed representations of the pathogenesis of these disorders and, in addition, allow assessing the development of damage and adaptive mechanisms of the brain, which serves as a fundamental basis for improving the methods of their diagnosis, treatment, and prevention [1-4]. Cardiovascular and cerebrovascular diseases hold leading positions in the structure of morbidity and mortality worldwide. About 7 million people die from cardiovascular diseases every year, and about 6 million people – from cerebrovascular diseases. Up to 85% of all strokes are due to cerebral ischemia [5,8]. In Russia, the incidence of stroke ranges from 460 to 560 cases per 100,000 population [5].

Modeling of hypoxic cerebral ischemia

The the most commonly used models of hypoxic cerebral ischemia was described in 1960. For its implementation, 7-day-old rat pups underwent unilateral ligation of the common carotid artery, followed by 3-hour inhalation of a hypoxic mixture containing 8% oxygen. In this case, a unilateral infarction occurs in the cerebral hemispheres, and the area of damage is localized in the periventricular regions of the brain, more often in the neocortex and hippocampus [14]. In our opinion, models of total cerebral ischemia are suitable for reproducing an atherothrombotic pathogenetic variant, while models of focal, multifocal, and hypoxic ischemia allow studying the development mechanisms and consequences of cardioembolic and lacunar types of cerebral infarction increasingly [12]. Models of total, subtotal, and partial cerebral ischemia are quite simple to implement, but their results are more difficult to extrapolate to humans, because focal ischemia is more typical for them. The model of total cerebral ischemia is suitable for reproducing anoxic brain damage during cardiac arrest [16]. Adequate models of cerebral ischemia contribute to detailing the pathogenesis of cerebrovascular diseases and are the basis for improving their diagnosis, treatment, and prevention, but the validation of these models still remains an important question, since they are not always able to reflect all those disorders of higher nervous activity, that occur when the human cerebral cortex is damaged, especially those associated with the second signaling system [13]. It is important to note that the most adequate models are not always feasible due to the lack of technical capabilities, while easy achievable models (subtotal and partial cerebral ischemia) are less adequate to the pathology developing in humans [6,7].

Modeling of cerebral anoxia of respiratory genesis in rats

After cutting the skin along the midline of the neck from the chin area to the sternum, the neck muscles were bluntly loosened to the trachea, on which a ligature was applied for 30 minutes (subgroup 1) and 60 minutes (subgroup 2) – below the rharyngeal cartilage [9-16].

Assessment of action in models of hypoxic hypoxia

Hypoxic hypoxia is based on a decrease of p02 in the inhaled air, achieved in different ways: 1) by an acute decrease of p02 while keeping the total partial pressure of air unchanged (normobaric hypoxia); 2) by an acute decrease of p02 while decreasing the total partial pressure of air (hypobaric hypoxia); 3) by a gradual decrease in oxygen content in ambient air through respiration (hypoxia with hypercapnia in a hermetic volume) [10-12].

Acute normobaric hypoxia (ANH)

The ANH is simulated in a flowing pressure chamber using a gas mixture (96–97% N_2 + 3–4% O_3) at an ambient temperature of 18–20 ºC with a CO_2 absorber (30% KOH solution) and a flow rate of at least 10 L/min in the first minute, and 1.5–2 L/min in the rest of the

experiment. 40–60 minutes after injection, the animals are placed in a sealed chamber. A gas mixture of the specified composition is supplied into the chamber in a fixed manner. The death of the animals is recorded [14-16].

Acute hypobaric hypoxia (AHH)

The simulation of AHH is carried out in a flowing pressure chamber with a CO_2 absorber (30% KOH solution) at an outside temperature of 20–22 °C. The experiments are carried out at the lowest atmospheric rarefaction at which all animals die ("death ground"). For mice, it is at an air vacuum of 170–186 mmHg (approximately corresponding to an altitude of 10,500–11,000 m). For rats, it is 145 mmHg (11,500–12,000 m). The average survival time at altitude depends on the rate of "ascent" (rarefaction). The higher it is the shorter is the survival time of animals at altitude. The most common ascent rate is 50 m/s. Very high ascent rates (180 m/s; ascent to altitude in 1 min) simulate hypoxia with little or no urgent adaptive reactions. At speeds of 36 m/s and below, on the contrary, they are evident and give a significant variation in the data [9-15].

Hypoxia with hypercapnia in a hermetic volume (in an enclosed space)

This form of hypoxia does not require sophisticated hardware to reproduce. Animals (preferably mice) are placed one by one in glass jars of equal volume, which are hermetically sealed. As the animals consume oxygen, the concentration of oxygen in the jar decreases, causing their death [11-13].

Acute hemic hypoxia (AHEH)

AHEH is based on a decrease in the oxygen capacity of haemoglobin. It is caused in three ways:

1) conversion of oxyhemoglobin to carboxyhemoglobin;

2) conversion of oxyhemoglobin to methemoglobin;

3) bloodletting.

Only the first case (1) simulates hemic hypoxia in its pure form. In methemoglobinemia (2) there is a combination of hemic and tissue hypoxia, which is confirmed by the high correlation coefficient between this model of AHEH and AHH (Table 1). In case 3, there is an additional strong effect on the vascular and respiratory centres. However, both latter forms of hypoxia are quite common in clinical practice. Therefore, they can be used as additional models of hypoxia in the screening of antihypoxics [2-9].

Carboxyhemoglobinemia (animal poisoning by carbon monoxide)

The experiments are carried out on non-pedigreed animals (mice, rats) 40–60 min after the substance has been injected. The animals are placed in a chamber, which is hermetically sealed, and a gas mixture containing CO (5–20 mg/L or 0.4–1.6%) is supplied into it. The supply rate of the mixture is 10–12 litres in the first minute and 1.5–2 L/minute thereafter. Inoculation time at 5 mg/L is 60 min, at 20 mg/L –15 min. Optimal modes are 15 mg/L for 20 min and 10 mg/L for 30 min.

The mortality of mice is 8–15%. The effectiveness of the antihypoxic protection of the tested substances is assessed by an increase in the survival rate of the animals compared to the control, and (necessarily) by the carboxyhaemoglobin content of the blood [2-7].

Methemoglobinemia (poisoning by methaemoglobin-forming agents)

Many substances capable of converting oxyhaemoglobin to methaemoglobin, both in vivo and in vitro, have been described. To simulate this type of hemic hypoxia, $NaNO_2$ sodium nitrite is most commonly used, which causes methemoglobinemia in all laboratory animals (rats, mice, cats, rabbits, dogs). It is less expensive to carry out experiments on mice. $NaNO_2$ is injected subcutaneously at a dose of 200–225 mg/kg, which causes 100% animal death after 27–30 minutes. A second possible option for modelling methaemoglobin formation is the use of aniline (in rats at a dose of 440–500 mg/kg). To assess the antihypoxic action of CS in this model, they are administered 30 min before methemoglobin formation. The effectiveness of the antihypoxic action of CS is assessed by the change in the survival time of the animals relative to the control [5-8].

Acute histotoxic hypoxia (AHTH)

The direct interaction of various poisons with cytochrome oxidase, an enzyme of the terminal site of the respiratory chain, leading to the suppression of its activity, is the basis of AHTH. Typical inhibitors that cause histotoxic hypoxia are hydrocyanic acid (HCN) and its salts – cyanides (KCN, NaCN, etc.). They can be used to induce AHTH in all laboratory animals. The most commonly used for this purpose is KCN, which is injected subcutaneously or intraperitoneally in a dose that results in severe oxygen deprivation with lethal outcome. The lethal dose of KCN in mice and rats is 8–10 mg/kg when injected subcutaneously, 2 mg/kg – in rabbits. The $LD\ of_{50}$ for mice is 5.4 (4.6–6.2 mg/kg). An aqueous sodium nitroprusside solution at a dose of 20–25 mg/kg injected intraperitoneally causes death of mice in 100% of cases within 15–20 min after injection. The antihypoxic activity of CS in the nitroprusside model and its efficacy are evaluated in the same way as in the cyanide model [9-12].

Cardiac ischaemia (anoxia) is modelled by insertion of foreign bodies into the coronary lumen, temporary clamping or ligation of the descending artery branch at the border between the upper and middle third of the coronary artery, injection of pituitaryrin, etc. The result is myocardial infarction, which is preceded by abrupt morphological and biochemical changes in the heart muscle and in the whole organism. Myocardial infarction is reproduced in both large and small laboratory animals. In rats strapped to a machine, the thorax is opened and the descending branch of the left coronary artery (under the auricle of the left atrium) is ligated under a mild ether anaesthetic. The muscle and skin tissue are sutured with several stitches, and the wound is treated with iodine solution [5]. After arterial ligation, there are abnormalities in ECG (ST interval shifts from isoline and T wave) and cardiac energy metabolism,
after 4 hours the heart muscle infarction zone reaches its maximum: the effect of antihypoxant on necrosis zone formation, development of early postocclusive arrhythmias, ECG, and animal survival are evaluated [12]. Thus, the methodological approaches to modeling cerebral hypoxia outlined in the article will serve as a fundamental basis for further study of approaches to the prevention and treatment of cerebrovascular pathology

List of references:

1. Atchaneeyasakul, K., Guada, L., Ramdas, K., Watanabe, M., Bhattacharya, P. et al. (2016). Large animal canine endovascular ischemic stroke models: a review. *Brain* Res. Bull. 127, 134–140.
2. Autophagy and hypoxic ischemic brain injuries LI Yong-Qiang, FU Su, WANG Lai, LIU Bin, SHI Zhen-Yu*, DENG Jin-Bo* Institute of Neurobiology, Nursing College, Henan University, Kaifeng 475004, China
3. Boehme AK, Esenwa C, Elkind MS. (2017). Stroke risk factors, genetics, and prevention. Circ Res; 120 (03) 472-495
4. Bombardier CH, Rimmele CT, Zintel H. (2002). The magnitude and correlates of alcohol and drug use before traumatic brain injury. Arch Phys Med Rehabil. 2002;83(12):1765–1773.

5. Bon, E.I. (2023). Adaptation of the Brain to Hypoxia / E.I. Bon, N.Ye. Maksimovich, L. I. Vishnevskaya // *J. Clin. & Commun Med*. – Vol. 5(2). – P. 540-543.
6. Bon, E.I. (2023). Morphological Changes in Neurons of The Parietal Cortex and Hippocampus of Rats with Partial Cerebral Ischemia / E.I. Bon, N.Ye. Maksimovich. S.M. Zimatkin, A.R. Lelis // Archives of Immunology Research and Therapy. V. 2(1).– P. 1-5.
7. Brinjikji W, Lanzino G, Cloft HJ, Siddiqui AH, Boccardi E, Cekirge S, et al. (2016). Risk factors for ischemic complications following pipeline embolization device treatment of intracranial aneurysms: results from the IntrePED Study. *AJNR Am J Neuroradiol* 37:1673.
8. Cykowski MD, Coon EA, Powell SZ, Jenkins SM, Benarroch EE. et al. (2015). Expanding the spectrum of neuronal pathology in multiple system atrophy. *Brain* 138: 2293–2309.
9. Feduto M.A. (2023). Modeling of Cerebral Anoxia of Respiratory Genesis in Rats / M.A. Feduto, N. Ye. Maksimovich, S.M. Zimatkin, E.I. Bon, A.I. Grichenko, I.N. Burak // *Archives of Urology and Nephrology*. № 2(1). – P. 1-4.
10. HK Kim Experimental models of cerebral ischemia. Acta Anaesthesiol Scand Suppl, 111 (1997), pp. 91-92
11. Karch CM, Goate AM. (2015). Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry; 77.
12. Maksimovich, N.Ye . (2023). Balance of The Brain of Rats with Cerebral Ischemia with The Introduction Of L-Name, L-Arginine, And Omega-3 Polyunsaturated Fatty Acids / N.Ye. Maksimovich , E.I. Bon, E.I. Troyan, N.V. Kokhan // *Neurons and Neurological Disorders*.Vol. 2(1). – P. 1-4.
13. Maksimovich, N. Ye. (2023). Mediators of the Nervous System Kinds Characteristic / N. Ye. Maksimovich, E. I. Bon, N. V. Kohan // *Biomed J Sci & Tech* Res.Vol. 48(4). – P. 39982-39982.
14. Siegler JE, Albright KC, George AJ. et al. (2017). Time to neurological deterioration in ischemic stroke. *Med Student Res J*. 4: 18-24
15. W. Sun et al. (2021). A modified four vessel occlusion model of global cerebral ischemia in rats. *J. Neurosci*. Methods.
16. Xu K, LaManna JC. (2014). Short-term hypoxic preconditioning improved survival following cardiac arrest and resuscitation in rats. *Adv Exp Med Biol* 812:309–315

DOI:10.31579/2637-8892/281