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Mini Review

Artificial Human Hibernation: From Hypothermia to Pharmacological Hypobiosis. Part I. History of Hypothermia

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Abstract

This article is a literature review of the development of human hibernation and highlights the historical aspects of the formation of hypothermia as a method of controlling human metabolism and neuroprotection of the brain in critical conditions.

Keywords: Hibernation; Hypothermia; Hypobiosis; Metabolism

Introduction

Hibernation is a behavioral, physiological, and molecular adaptation specific to various species of mammals, which allows poikilothermic mammals to tolerate the limited availability of resources found in extreme conditions [11]. During the winter hibernation, animals experience numerous periods of numbness, which are interrupted by short periods of euthermia up to 35 - 36°C. Numbness can be divided into three phases: onset, maintenance and excitation, followed by a period between attacks of euthermia. During the onset and maintenance of numbness in animals, there is a general slowdown in metabolism, a decrease in body temperature, a decrease in heart rate, a decrease in cerebral blood flow of up to 10%, a decrease in oxygen consumption, a decrease in respiratory rate, and suppression of immune responses [6,11]. At the same time, the duration of hibernation of an animal depends on the level of brain metabolism [9]. During waking up or during short periods of euthermia, rapid reperfusion of blood occurs, accompanied by a huge consumption of oxygen and an increase in body temperature. Inflammatory and immune responses resume, and the ability to remove free radicals increases [15,22]. Intermediate euthermia is characterized by metabolism, blood flow and body temperature characteristic of a homothermal mammal of a similar size [10].

In humans, as a result of the development of a shock state, responses occur in the form of centralization of blood circulation, increased energy requirements of the brain and other tissues. Subsequently, when it is impossible to provide adequate highly specialized medical care at the early stage, the human brain passes through a hypermetabolic state into catabolism. During catabolism with oxygen deficiency, anaerobic type of respiration is noted, which subsequently leads to the death of neurons. At the macroscopic level, these mechanisms manifest themselves in the form of diffuse cerebral edema and the gradual death of the gray matter of the brain, as the structure least adapted to hypoxia. Therefore, many emergency and intensive care specialists are trying to achieve a hibernation state in the patient in order to be able to provide more effective care.

Artificial hibernation or hypobiosis - an analogue of the natural hibernation of mammals [2,20], today it can solve a number of issues in medicine of critical conditions. Due to a decrease in the level of metabolism in critically ill people, it becomes possible to add the time required to provide highly specialized medical care with minimizing damage to perfusion-dependent organs (brain, kidneys, pancreas).

Achieving hibernation is possible by using therapeutic hypothermia, drugs or combination of these two methods.

The first mention of hypothermia as a treatment dates back to the 5th millennium BC and is described in the ancient Egyptian treatise on medicine and surgery "Edwin Smith Papyrus". Hippocrates recommended using snow and ice to stop bleeding. Complete body cooling was used to treat tetanus in the 4th and 5th centuries BC. [14,24]. At the end of the 18th century, a Scottish physician, Dr. James Kerry, conducted the first systematic experiments in humans to determine the effect of various cooling methods on body temperature, pulse, and respiration. He successfully used body cooling using cold water (hydrotherapy) to treat several clinical disorders and documented body temperature and information about the state of health and illness in the experiment [24]. Russian doctors in the XIX century used hypothermia therapeutically, covering people with snow, with subsequent attempts to revive them [23]. Baron de Larry, Napoleon's chief surgeon during the 1812 campaign, used cold anesthesia to amputate limbs. He noticed that the frozen soldiers, who were closer to the fire, died faster than those who remained in a condition of hypothermia [24]. In 1865, the Russian scientist Walter A.P. during his experiments showed pharmacological protection by lowering the temperature of rabbits to 20°C, followed by warming [1]. In 1892, Sir William Osler at Johns Hopkins University experimented with hypothermia in patients with typhoid fever and reported a decrease in mortality from 24.2% up to 7.1% [24].

In 1938, Dr. Temple Fei repeated therapeutic hypothermia in a famous experiment when he chilled a patient with insurmountable pain from metastatic breast cancer to 32°C for 24 hours ("cooling" as he described in his publications). This was followed by an era of "analgesic" hypothermia in patients with metastatic malignancy. In 95.7% of these patients, a decrease in pain symptoms was noted. Dr. Temple Fay invented one of the earliest "cooling blankets", which is a special isolated mattress between the bed and the "zipper" blanket containing rubber tubes for the continuous circulation of chilled fluids. Adding a hood made it possible to apply cold to the head. Dr. Fay also successfully performed intracranial implantation of a metal capsule to provide local tumor hypothermia [4].

The "neuroprotective" era of hypothermia can be considered the period from 1949 to 1960. Bigelow and his colleagues recorded a positive effect of low temperature on the animal brain during cardiac surgery [6]. Rozomoff and others have demonstrated that hypothermia reduces cerebral blood flow and oxygen consumption and has a beneficial effect on intracranial pressure (ICP) in dogs with experimental traumatic brain injury (TBI) [17]. At about the same time, hypothermia was successfully used in surgical treatment of intracranial aneurysm [7].

The first clinical study of hypothermia in the treatment of comatose patients after cardiac arrest was published in 1958. It reported 50% survival (6 out of 12) for patients with hypothermia up to 33°C compared with 14% (1 out of 7) patients in normothermic group [25]. In 1964, hypothermia became part of the first published algorithms for cardiopulmonary resuscitation (CPR) by Peter Safar, who advocated cooling patients for 30 minutes after the resumption of spontaneous circulation, if there were no signs of recovery of the central nervous system [18]. After that, favor in hypothermia decreased due to the difficulty of managing side effects such as arrhythmia, coagulopathy and infection. So, moderate hypothermia (28 - 32°C) was used, because such a temperature was considered the most favorable at that time [14].

At the same time as foreign colleagues in the early 60s, scientists from the USSR (Kupriyanov PA 1959, Kolesnikov AS., *et al.* 1961, Burakovsky VI., *et al.* 1961, Vishnevsky AA., *et al.* 1961) used the method of deep hypothermia in open heart surgery, but was it abandoned due to acute circulatory disorders at a cooling depth. A group of researchers led by V. Sergievsky used deep hypothermia (21 - 25°C) in 70 patients during surgical treatment of congenital heart defects, but subsequently abandoned this technique due to hemodynamic disturbances. The last who tried to use deep hypothermia (20 - 22°C) in the USSR were the Latvian surgeons VY Volkolakov and AT Latsis, but also refused to use it for the above reasons [1].

From the beginning of the 70s to the end of the 20th century, European and American scientists conducted comprehensive studies on the neuroprotective properties of moderate hypothermia. At the same time, in the 70s - 80s in the Novosibirsk Research Institute of Blood Circulation Pathology of the Ministry of Health of Russia under the guidance of E. N. Meshalkin, a hypothermia technique was developed and the method of perfusion-free hypothermia with the definition of indications and contraindications was improved. Litasov E.E. and Postnov V.G. determined by the mid-90s the possibility of perfusion-free hypothermia during cardiac surgery. In 1991, L. M. Bulatetskaya showed that with general cooling to 24°C, the temperature of the brain, especially of the superficial departments, is 18°C, which increases the antihypoxic protection of the brain [1]. It is worth noting that in the 90s the effectiveness of moderate hypothermia was shown in animal models after CPR, with cerebral ischemia and bacterial meningitis [12,13,16]. Also, in the 90s, several studies were conducted on the use of mild hypothermia in (TBI) as a method of treating intracranial hypertension. The prerequisites for the use of mild hypothermia in patients after CPR were laid [19].

In 2002, the results of two prospective randomized controlled trials in patients with anoxic post-TBI after community-acquired CPR were published. A study by Bernard., *et al.* demonstrated a high survival rate for patients in the group with hypothermia (49% compared with 26% of patients who did not have hypothermia (OR = 5.25 in favor of hypothermia) [5]. The second study evaluated the survival rate of 28 patients after CPR (55% vs. 39% of the control group), as well as low mortality after 6 months (41% vs. 55%) [21].

Thus, the third stage of research in the field of hypothermia using more modern technologies is accounted for the beginning of the XXI century.

However, the problem of the safety of using therapeutic hypothermia with the minimization of side effects has not been resolved yet, that limits its use in medical practice. The idea of lowering the human body temperature is to reduce metabolism and protect the main organs (brain, kidneys, heart) from hypoxia. Since the late 60s, the domestic scientist N. N. Timofeev devoted most of his work to creating a safe method of artificial hibernation and protecting the human body from cold death [3].

At the beginning of the XXI century, many works of biologists and physiologists on the study of hibernation of mammals were published. Also, a number of works offer a theoretical solution to the problem of creating hibernation in humans. However, most of the models come down to controlling metabolism through temperature, but not vice versa.

Conclusion

Thus, in this series of articles, both methods of reducing metabolism will be considered: external temperature changes (hypothermia) and pharmacological suppression (hypobiosis).

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