Review

The role of hypoxia in mental development and in the treatment of mental disorders: A review

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Summary **The purpose of this review is to trace the trends in studying and applying hypoxia in the field of mental problems. A literature review was conducted using the PubMed database, with a time-frame extending to October 2010. According to the neurodevelopmental model of mental disorders, abnormalities in brain development during pre- and perinatal life lead to psychotic manifestation in adolescence or young adulthood. Studies show that hypoxia plays an important role in almost any risk factor related to brain development in early life: pre-eclampsia, infection/inflammation, hypoxia/ischemia, preterm birth, and asphyxia at birth. The cited data show trends in using hypoxia, especially in the form of intermittent hypoxic training, for the treatment and prevention of mental disorders, and trends in using it for increasing mental capacity in animals.**

Keywords: Hypoxia, mental disorders, treatment, prevention, mental capacity

1. Introduction

Mental disorders are devastating illnesses affecting millions worldwide, with significant financial and emotional burdens for patients, their families, and society. The total annual cost of depression in Europe was estimated at €118 billion in 2004 (*1*), the estimated total societal cost of schizophrenia for England was £6.7 billion in 2004/05 (*2*).

About 30 years ago, a neurodevelopmental model of mental disorders, as a hypothesis, was proposed (*3*). It has provided great impetus to the psychiatric research community and is now widely accepted and developed. This model suggests that abnormalities in brain development during pre- and perinatal life lead to psychotic manifestation in adolescence or young adulthood (*3-12*).

It is known that abnormalities in brain development during pre- and perinatal life arise under the influence of different stress factors. The role of hypoxia in stress factors such as hypoxia/ischemia and asphyxia is well known. The role of hypoxia in other stress factors, however, is not well understood, though hypoxia, according to modern conceptions, is included in the pathogenesis of almost any disorder. The literature is also scant on the use of hypoxia in the prevention and treatment of mental disorders. There are many poorly understood facts, connecting hypoxia and mental disorders; coordinating these facts with the neurodevelopmental model would be desirable.

The aim of this review is to trace the trends in studying and applying hypoxia in the field of mental problems, particularly: *i*) the role of hypoxia in abnormal brain development; *ii*) the possibilities of hypoxia for increasing mental capacity; and *iii*) the possibilities of hypoxia for treatment and prevention of mental disorders. A literature review was conducted using the PubMed database, with a time-frame extending to October 2010. More than 11,000 titles, about 400 abstracts, and some full-text articles were reviewed.

2. Hypoxia in the etiology of mental diseases

Environmental insults during early brain development may have long-lasting consequences for adult brain functioning. The following important stressful environmental risk factors that influence the future development of mental disorders were claimed in the studied literature: hypoxia (hypoxic hypoxia), ischemia, asphyxia, infection, inflammation, pre-eclampsia,

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preterm birth, and maternal psychological stress during pregnancy. Reviews for these risk factors have been done by (*13-16*).

Hypoxic hypoxia (breathing air with low oxygen content) and circulatory hypoxia (ischemia, asphyxia) are widely used in animal experiments to mimic preterm birth and other events resulting in neurodevelopmental disability, including schizophrenia and depression. Perinatal sublethal hypoxia, hypoxic/ischemic insults were usually used in experiments that show: *a*) significant alterations in corticogenesis: failure of brain growth, progressive cerebral ventriculomegaly, decreased subcortical white matter and corpus callosum size, and decreased cortical volume (*17*); *b*) alteration in the production and maintenance of glial and neuronal cells (*18*); *c*) white matter damage (*19*); *d*) loss of cortical neurons (*20*); *e*) modifications in corpus callosum, cingulum, and fimbria of the hippocampus (*21*); *f*) impaired development of neural processes and connections in the hippocampus, cerebellum, and visual cortex (*22*); *g*) reduced brain weight, ventriculomegaly, reduced basal ganglia volume and absence of astrogliosis (*23*); *h*) facilitation of proliferation of neural stem cells (*24*); *i*) lowered body and brain weights, as well as decreased cortical volumes of newborn rats; however, hypoxic rats had increased neuronal density and significantly more cortical neurons (*25*); and *j*) changes related to the subventricular zone, hippocampus, and dentate gyrus (*26-31*).

Several articles contained epidemiological data (*32-34*).

In a prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia (*32*) was found that the odds of schizophrenia increased linearly with increasing number of hypoxia-associated obstetric complications and that this effect was specific to cases with an early age at onset/first treatment contact.

In a 19-year longitudinal study of hypoxic-ischemia-related fetal/neonatal complications was found (*33*) that these complications were associated with a doubling of the risk of developing a psychotic disorder.

Signs of asphyxia at birth are associated with an increased risk of schizophrenia in adults, according to a population-based case-control study (*34*). This study used 524 cases of schizophrenia and 1,043 controls.

Tissue (histotoxic, cytotoxic, cytopathic) hypoxia appears when tissues are unable to use oxygen despite normal oxygen delivery. This type of hypoxia is involved in infection/inflammation during pregnancy, which leads to pre-eclampsia and preterm birth. Each of these conditions leads to an increased risk for psychoses among adult offspring (*35-39*).

The main pathological process of infection/inflammation is widely recognized as the inflammatory response syndrome (*15,40,41*), which is based on tissue hypoxia. The cells under the tissue hypoxia behave as if there is too little oxygen because of an inflammation-induced alteration in cellular function, not because there is too little oxygen for cellular function (*42*). The studies show, in particular, that: *a*) hypoxia and the innate immune response are 2 adaptive mechanisms by which organisms respond to perturbation in organ function, playing a major role in spontaneous abortion, intrauterine growth restriction, pre-eclampsia, and preterm delivery (*43*); *b*) the placenta expresses a variety of pro- and anti-inflammatory cytokines, adipokines and cytokine-like angiogenic growth factors, production of which is altered in pre-eclampsia, driven (at least in part) by hypoxia (*44*); *c*) the underlying pathology of pre-eclampsia is thought to be a relatively hypoxic or ischemic placenta (*45*); *d*) infection-associated immunological events in early fetal life may have a stronger neurodevelopmental impact compared to late pregnancy infections (*46*); and *e*) in utero exposure to bacterial infection can severely alter fetal cardiovascular function, resulting in dysregulation of cerebral blood flow and subsequent hypoxic-ischemic brain injury (*16*).

Maternal psychological stress during pregnancy is probably also accompanied by hypoxia (*47-49*), but this association should be analyzed more scrupulously.

The earlier cited data show that hypoxia is involved in almost any important stressful environmental risk factor during early life, leading to excessive pathologic neurogenesis. Such pathologic neurogenesis becomes apparent from the changing size of the defined neuronal network zones or their structure, for example, increased neuronal density. Furthermore, pathologic neurogenesis in mental disorders is clearly routinely seen in psychosurgery, the task of which is just to ablate pathologically changed brain zones. Pathologic neurogenesis is probably connected with the abnormal formation of neural network elements. For example, "the specificity of synapse formation requires the precise execution of multiple developmental events, including cell fate specification, cell migration, axon guidance, dendritic growth, synaptic target selection, and synaptogenesis" (*50*). The changes in the brain stimulated by pathologic neurogenesis may lead to abnormal communications in the neural network; which causes abnormal associations, ideas, and acts, *i.e.*, mental disorders.

3. Hypoxia in increasing mental capacity

It was shown earlier that acute hypoxia in early life is a trigger for anomalous brain development, which leads to psychotic manifestation in adolescence or young adulthood. The neurodevelopmental model clearly suggests that moderate hypoxia in early life may be a trigger for a moderate increase in brain development leading to increased mental capacity, probably to the level of genius and, sometimes, to madness.

Proverbs, adages and quotes that make the connection between genius and madness have existed in different languages for hundreds or even thousands of years as the following examples demonstrate: "There is a fine line between genius and insanity"; "There is just one step from genius to madness" (Pushkin); "There is no great genius without a mixture of madness" (Aristotle).

The phenomenology and psychopathology of genius was considered (*51*). The author noted that the relationship between genius and madness has been a subject of interest since the beginning of critical and philosophical thinking. Thus, Aristotle, in the Problemata, asks himself "Why are all extraordinary men in the fields of philosophy, politics, poetry and art melancholic?" adding afterwards "... and some of them in such a way that they may suffer from pathologic manifestations whose origin is in the black bile". In the past decades the German author Tellenbach studied the personalities of several geniuses, both from fiction, such as Hamlet, and from reality, such as the writer von Kleist, concluding that they suffered from a specific form of depression that he called "Schwermut" (melancholy), which was supposedly different from the narrowly defined illness of depression. Other work done on this subject is the extensive study by the North American author Kay Jamison, who, after researching the biography and the tree of a long list of writers, composers and musicians, concluded that all of them had suffered to some degree from a bipolar disorder. This author finds that, together with other essential features, the geniuses always show forms of experiencing and/or of behaving which do not fall within the range that is considered normal, although they can not always be classified as "pathological".

There are many other examples of geniuses who had suffered from mental malfunctions: Rembrandt (*52*), Vincent van Gogh (*53*), and Leo Tolstoy (*54*).

Increased mental capacity in humans may be modeled in animal experiments, where it should be reflected as increased development of conditioned reflexes. Some articles (*55-59*) suggest this possibility.

As was shown by Meerson *et al.* (*55*), regular training of adult rats in the hypobaric chamber to intermittent effect of altitude hypoxia causes a pronounced activation of protein synthesis and an increase of the DNA concentration in the brain. This activation is accompanied by a better preservation of developed conditioned reflexes of passive avoidance and an increase in the resistance of time relations to the electric shock effect.

It was found that neonatal exposure to intermittent hypoxia enhances the performance of mice in water maze and in 8-arm radial maze tasks (*56*). Intermittent hypoxia was simulated in a hypobaric chamber at 2 km (16.0% O_2) or 5 km (10.8% O_2) for 4 h/day from birth to 1, 2, 3, or 4 week(s), respectively.

Lu *et al.* (*57*) state that mild intermittent hypoxia (16.0% O_2, 4 h/day for 4 weeks) is known to markedly enhance spatial learning and memory in postnatal developing mice. From this observation, they found that Spine-associated Rap-specific GTPase-activating protein is functionally required for synaptic plasticity and contributes to this intermittent hypoxia-induced enhancement.

Shao *et al.* (*58*) investigated the effect of hypoxic preconditioning on spatial cognitive ability in mice after acute and repeated hypoxic exposures. The tolerance time was progressively prolonged as exposure went on.

It was found that conditioning-like brief neonatal hypoxia (100% N_2, 5 min) improved cognitive function and brain tissue properties (*59*). Marked gender dimorphism in adult rats was observed. It was proposed that brief neonatal hypoxia may exert long-term beneficial effects through stimulation of neurogenesis.

The cited experimental animal data may indicate that the stimulating influence of hypoxia is the basis for increased mental capacity, probably, to the level of genius. This would occur very rarely, when the numerous parameters of hypoxic influence combine in an optimal manner. Unfortunately, none of these studies (*55-59*) made even casual mention of the connection between increased mental capacity and mental disorders. No articles were found in which direct research was done on the dependence of mental development (normal, increased, mad) as a function of the power of hypoxia. Such a research could be useful, for example, in breeding smart dogs for special services.

4. Hypoxia in the treatment and prevention of mental diseases

The effects of rarefied air on an organism have been known for a centuries, but the first scientific studies appeared at the end of the 19th century.

It was found much later that breathing air with low oxygen content can be used as a method of hypoxic stimulation. This method is also known as intermittent (interrupted) hypoxic training (therapy) (IHT), normobaric hypoxic training (therapy), hypoxytherapy, and has been used by about 2 million patients for the last 30 years. This drug-free method is almost without contraindications and is applied to help recover from disorders such as bronchial asthma, insomnia, cardiovascular, obstetric, and gynecological disorders, and depression (*60-62*). This method was officially recommended in medicine (*63*) and also applied to increase physical working capacity and endurance, especially in sports (*64,65*). Much literature may be found on the web sites *www.go2altitude.com* (mostly sport) and *www.bionova.ru* (mostly medicine).

The main idea of this method is to fight with hypoxia through hypoxia, *i.e.*, through previous

adaptation to hypoxia by minor, harmless hypoxia. Generally, this approach is similar to the idea of training for any harmful factor, for example, to infection through vaccination. Another training example is jogging, where a demand (load) hypoxia is created. Hypoxia accompanies almost any pathological process and thus hypoxic training to hypoxia is very important.

There are three basic mechanisms underlying the beneficial effects of IHT (*62*): regulation of respiration, free-radical production, and mitochondrial respiration. It was found that IHT induces increased ventilatory sensitivity to hypoxia, as well as other hypoxia-related physiological changes, such as increased hematopoiesis, alveolar ventilation and lung diffusion capacity, and alterations in the autonomic nervous system. Due to IHT, antioxidant defense mechanisms are stimulated, cellular membranes become more stable, Ca^{2+} elimination from the cytoplasm is increased, and O_2 transport in tissues is improved. IHT induces changes within mitochondria, involving NAD-dependent metabolism that increase the efficiency of oxygen utilization in ATP production.

Hypoxic training is not, however, a method of treatment a specific disorder. Rather, hypoxic training is a method to improve general resistance the organism, increasing the possibility of resisting unfavorable factors. For example, the effects of hypoxic training (10% O_2) on increasing the compensatory capabilities of organisms were researched by Strelkov *et al.* (*64*). Experimental data on animals were provided for asphyxia, acute hypoxia with hypercapnia, hemorrhagic shock, physical load, tick-borne encephalitis virus infection, and intoxication by 8 different poisons. Clinical data were provided for gynecological and oncological patients. All data show significant and reliable increase in compensatory capabilities after previous hypoxic training/preconditioning.

The protecting effect of the hypoxic training as a preconditioning procedure was studied in different fields by other researches as well (*66-68*).

The following sections examine issues related to the use of different versions of hypoxic hypoxia for therapy/prevention of mental disorders.

4.1. *Sojourns in the high mountains*

In 1952-1954, expeditions with patients with schizophrenia were conducted in the area of Elbrus (Caucasus) (*69*). Positive but insufficiently strong results were obtained. The study author mentioned that the better result was obtained not when patients were stayed at the mountains, but when they climbed down. In the author's opinion, it was because patients, after acclimatization to the high mountains climate, were better able to use oxygen.

In 1961-1963, expeditions with patients with schizophrenia were conducted in Kirgizia, in the area of Tien Shan (*70-72*). A temporary summer hospital was organized at 3,540 m. Positive results were found for some forms of schizophrenia, but even better effects were observed when patients climbed to 4,000-4,200 m. Of interest among the reasons for those expeditions was the following: "We have noticed that there are extremely few psychiatric patients among the residents of the high mountains".

The effects of high altitude stay on the incidence of common disorders in man were described by Singh *et al.* (*73*). The study involved 130,700 men stationed on the plains between 760 m and sea level, and 20,000 men stationed at altitudes between 3,692 and 5,538 m from 1965 to 1972 (during the Indian-Chinese conflict). A significantly lower number of cases of most disorders, including psychiatric disorders, were found among the men at high altitude than among those at sea level.

4.2. *Hypobaric chamber*

A few articles have been published on studies in the hypobaric chamber. The use of such a chamber instead of sojourns in the high mountains was an attractive factor for the researchers.

Patients entered the hypobaric chamber together with the doctor (*74*). The pressure in the hypobaric chamber decreased gradually up to a "height" of 10,500 m. The doctor was forced to use an oxygen apparatus beginning at a "height" of 5,000 m, whereas patients tolerated the following rarefying easily. There was no "lifting" above 10,500 m, though there were no signs of unconsciousness in the patients. Each session lasted for 1-2 h, and occurred three times a week, for a total of 6-8 sessions on average. There were 16 patients, all with schizophrenia. Only transitory improvement occurred, mainly short-time disinhibition. (*Note*: The patients' amazing tolerance to hypoxia shows that their brains are probably in a condition of strong hypoxia. This important circumstance may be due to excessive pathologic neurogenesis, and further research is needed. – S.B.).

Similar research was performed by Kantorovich (*72*) with the same results.

It was found that intermittent hypobaric hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats (*75*).

4.3. *Normobaric hypoxytherapy*

Normobaric hypoxytherapy as an IHT is the most widespread version of hypoxic training found in general therapy and sport due to its availability and usability.

The first trials of this method in psychiatry were conducted in the United States (*76-80*), mostly with patients who were diagnosed with schizophrenia. The results were initially insignificant but encouraging, but eventually became negligible.

The detailed analysis of the procedure and equipment used in these trials (*81*) showed that the reason for the unsuccessful results was a weak hypoxic influence; improvements to the procedure and equipment were proposed. This conclusion should be considered in any future research on the treatment of mental diseases.

A positive experience in the treatment of depression by mild (9% O_2 and above) hypoxic hypoxia was reported (*82*).

The use of IHT in therapy of endogenous depressions was described by Karimulaev (*83*). The therapeutic procedure was as follows: breathing a hypoxic gas mixture of 10% O_2 through the mask for 3-5 min and then breathing atmospheric air for 3-5 min; this pattern continued for up to 120 min. This procedure has been used as a monotherapy in a group of 51 patients; a positive effect was achieved in 36 patients (71%). Therapeutic effectiveness was positively correlated with the speed of an approach of the therapeutic effect. Sufficient improvement was achieved after 3-4 weeks of treatment in the majority of the participants.

The effect of IHT on postschizophrenic depression has also been studied (*83,84*) with therapeutic effectiveness being achieved in 57% of patients.

4.4. *Hypoxic hypoxia as a preventive means*

Numerous studies have provided evidence for the brain-protective features of hypoxic hypoxia.

The effects of preconditioning using mild repetitive hypobaric hypoxia (360 Torr for 2 h on each of 3 days) have been studied in the learned helplessness model of depression in rats (*85*). The hypoxic preconditioning had a clear antidepressive action returning the behavioural and hormonal parameters to the control values and was equally effective as the antidepressant. The study authors considered the findings to suggest that hypoxic preconditioning is an effective tool for the prophylaxis of post-stress affective pathologies in humans.

The protective effects of hypoxic preconditioning on the development of depressive states in rat models were studied by Rybnikova *et al.* (*86*). Three episodes of intermittent preconditioning using hypobaric hypoxia (360 mmHg, 2 h) prevented the onset of depressive behavioural reactions, hyperfunction of the hypophyseal-adrenal system and impairments in its suppression in the dexamethasone test in rats following unavoidable aversive stress in a model of endogenous depression. The anxiolytic and antidepressant actions of hypoxic preconditioning in experiments on rats were no less marked than those of the tetracyclic antidepressant Ludiomil. The results obtained provide evidence that preconditioning with intermittent hypobaric hypoxia increases resistance to psychoemotional stresses, has marked anxiolytic and antidepressant effects and can be used for the prophylaxis of depressive episodes.

Hormonal mechanisms of neuroprotective effects of the mild hypoxic preconditioning in rats were also studied by Rybnikova *et al.* (*87*).

Hypoxic hypoxia has been found to prevent brain injury and to have a protective role in the central nervous system (*24*). Adult rats were exposed to "high altitudes" of 3,000 and 5,000 m for 4 h per day for 2 consecutive weeks. The study authors were convinced that the proliferation of neural stem cells in the subventricular zone and dentate gyrus may contribute to adaptive changes following intermittent hypoxia.

Regarding the routine practice in public health for the prevention of mental disorders, the most developed type of prevention is secondary prevention, *i.e.*, early intervention (*88-94*). Vaccination (*95,96*), improved prenatal nutrition (*95*) and prenatal multivitamin use (*96*) may be beneficial in primary prevention, but these means have not been shown to substantially prevent mental diseases. The pessimistic conclusion that has been drawn is that "primary prevention is beyond capacity of our present knowledge" (*88*). However, a trend is developing for solving the problem of effective primary prevention of mental diseases by the use of IHT.

As was examined earlier, pre-eclampsia and infection/inflammation during the prenatal period, as well as asphyxia at birth, are closely connected with hypoxia and are the most important triggers of future mental disorders. Therefore, successful treatment or prevention of these conditions will simultaneously prevent mental disorders; *i.e.*, IHT may be considered as a means for the primary prevention of mental disorders.

The research of the development of children born to mothers with pre-eclampsia who have been treated by normobaric hypoxia was conducted by Verbonol and Chizhov (*97*). A hundred women cured by IHT and 50 control women (given conventional treatment) were under care. IHT was carried out at 16-35 weeks of pregnancy and consisted of 8-30 sessions. Each session included 5 min of breathing a hypoxic gas mixture (10% O_2) through mask, interrupted by 5 min of breathing atmospheric air, with a total of 6 cycles in 1 h. All children were under care at birth and monthly during the first year of life. The following parameters were measured: percentage of premature births, Apgar scores, characteristics of physical and neuropsychic development, breastfeeding duration, percentage of children with allergic diathesis, hemoglobin content in child's peripheral blood, and prevalence of acute respiratory disorders. All measured parameters were significantly better in children whose mothers had been treated by IHT.

Oxygen metabolism kinetics was investigated in 90 pregnant females at high risk for pre-eclampsia and associated vascular disorders (*98*). Patients were

treated with IHT. The study revealed that initial disorders of tissue respiration featured compensatory stimulation of tissue oxygen consumption. In early signs of pre-eclampsia the consumption intensity was found to be diminished. During treatment there was evidence of normalization in oxygen metabolism. This treatment proved to be an efficient drug-free method of pre-eclampsia prevention.

The efficiency of preventive use of IHT in pregnant women at high risk of developing of pre-eclampsia was studied by Evgen'eva *et al.* (*99*). The authors focused on a decrease in the incidence of pre-eclampsia, especially its severe patterns, and perinatal mortality.

The use of IHT with 10% O_2 is not only absolutely harmless for the fetus and has no unfavourable effects on the course of the pregnancy or its outcome, but it is also accompanied by a significant increase in the mass of the placenta by 26.9-33.2% and the mass of the fetus by 8.5-12.2% (*60*). Many other clinical data to support the harmlessness of IHT are provided.

The use of IHT in obstetrics was reviewed by Tsyganova (*100*). The literature and the researcher's own investigations showed more successful delivery, less frequent occurrence of nephropathy, fetal hypoxia, premature labor, and better physical condition of newborns.

The use of IHT in obstetrics and gynecological practice was recommended by Russian Health Ministry (*101*).

Hypoxic influence was studied in experiments on pregnant animals (rabbits, rats) conducted during the last third of pregnancy using a hypobaric chamber (*102*). It was established that a moderate hypoxic influence during this period promotes the physiological maturing of the fetus, and the mass of the newborn animals was appreciably increased.

Infection/inflammation during pregnancy, as described earlier, is an important hypoxia-connected risk factor for future mental disorders. In the paper (*64*) infection was mentioned among the numerous harmful influences toward which IHT can increase resistance. Experimental data on mice infected with tick-borne encephalitis virus showed a survival rate of 51.7 ± 5.4% in the main group *versus* 33.3 ± 5.1% in the control group. Therefore, use of IHT for increasing resistance to infection is simultaneously a means for the prevention of mental disorders caused by infection.

Data from the literature (*60,97-101*) related to the general IHT procedure, particularly in obstetrical applications, suggest the following IHT procedure for prevention of mental diseases: one IHT session before pregnancy and one or two sessions during pregnancy after the 16th week. These data clearly show a trend for the successful use of IHT in the primary prevention of mental diseases, but additional studies are needed.

5. Conclusion

Hypoxia plays an important role in almost all environmental risk factors for future mental disorders, acting during early development and capable to stimulate mental disorders in adolescence or young adulthood as a result of pre-eclampsia, infection/inflammation, hypoxia/ischemia, preterm birth, or asphyxia at birth.

Hypoxia stimulates neurogenesis. Excessive pathologic neurogenesis becomes apparent from the changing size of the defined neuronal network zones or from changing their structure, for example, increased neuronal density. The changes in the brain stimulated by pathologic neurogenesis may lead to abnormal communications in the neural network, which causes abnormal associations, ideas, and acts, *i.e.*, mental disorders.

Although more studies need to be done, hypoxic hypoxia, especially in the form of IHT, may have applications in increasing mental capacity of animals and in the treatment and primary prevention of mental disorders.

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