



Oxygen, a key factor regulating cell behavior during neurogenesis and cerebral diseases

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Oxygen is vital to maintain the normal functions of almost all the organs, especially for brain which is one of the heaviest oxygen consumers in the body. The important roles of oxygen on the brain are not only reflected in the development, but also showed in the pathological processes of many cerebral diseases. In the current review, we summarized the oxygen levels in brain tissues tested by real-time measurements during the embryonic and adult neurogenesis, the cerebral diseases, or in the hyperbaric/hypobaric oxygen environment. Oxygen concentration is low in fetal brain (0.076–7.6 mmHg) and in adult brain (11.4–53.2 mmHg), decreased during stroke, and increased in hyperbaric oxygen environment. In addition, we reviewed the effects of oxygen tensions on the behaviors of neural stem cells (NSCs) *in vitro* cultures at different oxygen concentration (15.2–152 mmHg) and *in vivo* niche during different pathological states and in hyperbaric/hypobaric oxygen environment. Moderate hypoxia (22.8–76 mmHg) can promote the proliferation of NSCs and enhance the differentiation of NSCs into the TH-positive neurons. Next, we briefly presented the oxygen-sensitive molecular mechanisms regulating NSCs proliferation and differentiation recently found including the Notch, Bone morphogenetic protein and Wnt pathways. Finally, the future perspectives about the roles of oxygen on brain and NSCs were given.

Keywords: oxygen, neurogenesis, cerebral diseases, hypobaric hypoxia, hyperbaric oxygen

INTRODUCTION

Oxygen, as a significant substrate for energy production and cell metabolism, is essential for most of the life on earth and affects various aspects of life activities, including growth and development. It is interesting to note that the normal oxygen levels in the tissues are always substantially lower than 156 mmHg O₂ in the air we breath (Panchision, 2009): in the lung parenchyma and in circulation, the oxygen tension is ranged from 28 to 98 mmHg; in the eye (retina, corpus vitreous), from 7 to 35 mmHg; in the bone marrow, from 0 to 28 mmHg. These oxygen concentrations (7–35 mmHg O₂) are called “physiological hypoxia,” that is a steady state of physiological oxygenation or “*in situ* normoxia” (Ivanovic, 2009).

The brain is one of the heaviest oxygen consumers in the body, which accounts for 20% of total oxygen consumption (Masamoto and Tanishita, 2009). However, the oxygen levels in almost all the regions of brain are very low: 32 ± 4 mmHg in the thalamus, 27 ± 6 mmHg in the cerebral cortex, 20 ± 3 mmHg in the hippocampus, and 15 ± 3 mmHg in the corpus callosum in isoflurane-anesthetized rats (Ivanovic, 2009). In addition, the development of various organs of embryos including the central nervous system (CNS) takes place in low-oxygen concentration (Fischer and Bavister, 1993; Chen et al., 1999). Apart from this, oxygen levels in brain tissues are often altered during stroke (Liu et al., 2004), brain trauma (Valadka et al., 1998), and in the hyperbaric oxygen (HBO) environment (Balenane, 1982). Thus, the oxygen supply to brain must be precisely controlled in response to local demand induced by metabolic activity to prevent tissue hypoxia which would immediately lead to irreversible damages in brain functions (Masamoto and Tanishita, 2009).

This review will cover the cerebral oxygen tensions during neurogenesis and cerebral diseases, then the role of oxygen on the cellular behaviors of neural stem cells (NSCs) will be discussed. In addition, the involved molecular mechanisms will be talked about in the present review.

OXYGEN NICHE DURING EMBRYONIC AND ADULT NEUROGENESIS

OXYGEN NICHE OF NEUROGENESIS DURING EMBRYO DEVELOPMENT

The accurate data about oxygen content during the embryonic neurogenesis has attracted many researchers. During the pre-implantation period, the oxygen tensions were about 60 mmHg in oviducts of rabbits (Mastroianni and Jones, 1965), but less than 10 mmHg in uterus of rhesus monkeys (Maas et al., 1976), 5–50 and 25–50 mmHg in uterus of the hamsters and rats (Kaufman and Mitchell, 1990). After the implantation of embryos the oxygen tension in amniotic fluid was 10.9 ± 1.0 mmHg in the early gestation and 11.6 ± 0.7 mmHg in mid gestation of sheep (Jauniaux et al., 2000). During the late gestation, although the onset of placental gas exchange establishes, the P_{O₂} values for umbilical artery, vein, and amniotic fluid are still constrained below maternal venous levels (23, 30, and 12 mmHg, respectively; Eskes et al., 1983; Yeomans et al., 1985; Rurak et al., 1987; Jauniaux et al., 2000). In summary, the whole process of embryonic development is under the low-oxygen concentration.

The embryonic neurogenesis begins at the early gestation period when the placental gas exchanges have not been set up, and under very low-oxygen concentration (≤15.2 mmHg; Zhou, 2004). In the mid and late gestation, the density of cerebral vessels has become

an important factor which determines the oxygen niche of embryonic neurogenesis (Takashima and Tanaka, 1978). Takashima and Tanaka (1978) have investigated the development of cerebral vascular in human fetal brain and found that most of the perforating branches are short in the second trimester and develop with gestational age. In most of cerebral regions, the vessel density is low before 28 gestational week (GW), and then increased after this time point, e.g., the cerebral cortex, the subcortical white matter, and the basis pontis. In the other cerebral regions, the vessel density is high before 28 GW, and decreases or remains high after this time point, e.g., the deep white matter and putamen (Mito et al., 1991; Miyawaki et al., 1998). Thus, the development of blood vessels during the whole gestational period might parallel with the changes of cerebral oxygen niche.

The direct evidences about oxygen niche of embryonic neurogenesis were provided by Chen (Chen et al., 1999), utilizing the hypoxia marker EF5, a nitroimidazole derivative which binds covalently to protein, RNA, and DNA in cells exposed to a hypoxic environment (0.076–7.6 mmHg oxygen; Lord et al., 1993). They found that the neural tube in both the hindbrain and midbrain regions also stained strongly with the EF5 immunoreactivity, indicating that the oxygen tensions of these regions substantially below 7.6 mmHg (Lord et al., 1993). Lee You Mie also used the hypoxia marker, pimonidazole hydrochloride (Hypoxyprobe™-1), to indicate the hypoxic regions during embryonic development (Lee et al., 2001). They found that hypoxic regions detected by hypoxia marker exist on 8.5–9.0 day past copulation (d.p.c.) in folding neural tube and neuronal mesenchymal cells in mouse embryos. In the brain, the mesenchymal region was hypoxia marker-immunoreactive, suggesting that at this stage at least, highly proliferative cells may be localized in the low-oxygen tension. At day 9.5–11.5, the hypoxic regions in embryonic tissues were spread into neural tubes of telencephalon, diencephalon, and metencephalon including mesenchymal region of head. On 12.5 d.p.c., the hypoxic immunoreactive regions were clearly demarcated in the internal lining of the cranial flexure, myelencephalon, and choroid plexi, and in the center of maxillary prominence, where cells proliferate and differentiate (Lee et al., 2001). Those above investigations provided strong and direct evidences that the embryonic neurogenesis was under very low-oxygen tension.

OXYGEN NICHE OF ADULT NEUROGENESIS

The neurogenesis in the adult mammalian brain was first evidenced by Altman in the adult rat using *in vivo* ³H-thymidine administration (Altman 1962, 1969; Altman and Das, 1965, 1967). Direct demonstration of NSCs in the mature brain was provided by means of primary cell culture from dissociated brain tissue (Reynolds and Weiss, 1992). This discovery generated great expectations by raising the prospect of regenerative therapies for the treatment of CNS injuries such as those brought by ischemia or neurodegenerative disorders (Miller, 2006). Continuous neurogenesis from NSCs has been identified in two neurogenic germinal zones of adult brains: the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles (Suh et al., 2009). Such *in vivo* neurogenetic restrictions were formally demonstrated to arise from the tissular microenvironment, which led to the emerging concept of “neurogenic niche” (Moyses et al., 2008).

The “neurogenic niche” includes the vascular niche, the astrocyte niche, the neural net niche, and the molecular pathway niche (Suh et al., 2009). However, the “oxygen niche” of the adult neurogenesis has not been paid extensive attention until now. Shen et al. (2008) have found that the SVZ contains a rich plexus of blood vessels that snake along and within neuroblast chains. Cells expressing stem cell markers, including glial fibrillary acidic protein (GFAP), and proliferation markers are closely apposed to the laminin-containing extracellular matrix (ECM) surrounding vascular endothelial cells. Tavazoie et al. (2008) have also found that dividing stem cells and their transit-amplifying progeny were tightly apposed to SVZ blood vessels both during homeostasis and regeneration. They frequently contact the vasculature at sites that lack astrocyte endfeet and pericyte coverage, and regeneration often occurs at these sites (Tavazoie et al., 2008). It has also been found that the physical exercise could induce both of the angiogenesis and the neurogenesis in hippocampus (Van der Borgh et al., 2009). Taken together, all of the above researches indicated the significant role of the vessels as one of the important components of the neurogenesis niche, and may also implied that the higher oxygen tension around the vessels in SVZ and DG would be significant for the maintenance of the characteristics of the NSCs. While, our recent work have provided some direct data related to the above issues. We found that the P_{O₂} levels in ventricles are in a dynamic state and fluctuate in the range of 42 to 48 mmHg at a frequency of about 3 min. In hippocampus, the P_{O₂} levels in CA1 and hilus are very stable and maintain about 2 mmHg; while the P_{O₂} level in DG is dynamic and fluctuates in a range of 6–8 mmHg (Zhang et al., 2010).

CHANGES OF OXYGEN TENSION IN BRAIN TISSUES DURING DIFFERENT STATES/CONDITIONS

OXYGEN CHANGES IN BRAIN TISSUES DURING BRAIN INSULTS

The oxygen supply to brain might be influenced by various brain insults, which could lead to brain irreversible damages. Brain insults include stroke, trauma, subarachnoid hemorrhage (SAH), and so on, which produce changes in structure, pressure dynamics, chemical balance, and blood flow (Bader, 2006). Ultimately, the delivery of oxygen to the cranial vault may become compromised. The devastating primary insult creates structural damage to neurons, vessels, and cranial nerves as well as compression of the brain and vasculature. The resulting edema and pathological processes further compromise the delivery of blood flow and oxygen to the brain (Bader, 2006).

The P_{O₂} levels in uninjured brain tissue has been measured about 25–30 mmHg in white matter of frontal lobes (Sarrafzadeh et al., 1998), 20–40 mmHg in normal tissue (Hlatky et al., 2003). A lot of researchers have also investigated the changes of oxygen tension during brain insults, such as stroke, trauma, or SAH (Maas and Fleckenstein, 1993; Zauner et al., 1996; Doppenberg and Zauner, 1998; Liu et al., 2006). van den Brink et al. (2000) studied 101 comatose patients who had traumatic brain injury (TBI) and reported that the survivors had significantly higher P_{O₂} levels during the monitoring period than did the patients who died. Lower P_{O₂} levels were related to a greater risk for death (van den Brink et al., 2000). The investigators found that P_{O₂} of less than 15 mmHg for longer than 30 min or less than 10 mmHg for 10 min correlated with a statistically significant risk for death. In one study of 39 patients, the

investigators found that P_{O_2} of less than 15 mmHg correlated with a greater chance of death. A value of less than 6 mmHg at any time was associated with a greater risk for dying (Valadka et al., 1998).

Liu et al. (2004) investigated the effects of stroke on the cerebral oxygen tension. They measured both absolute values, and temporal changes of P_{O_2} in ischemic penumbra and core during ischemia and reperfusion in a rat model with the electron paramagnetic resonance (EPR) method. They found that pre-ischemic P_{O_2} values in ischemic core and basal ganglial penumbra of the anesthetized rats were 33.4 ± 6.0 mmHg. After MCAO, interstitial P_{O_2} in both core and penumbra dropped rapidly in the first 10 min, thence the rate of decrease slowed, and reached their respective lowest levels at 1-h postocclusion. The interstitial P_{O_2} values in penumbra were significantly higher than the corresponding values in the core, and were 10.7 ± 7.8 and 1.2 ± 0.7 mmHg at 1-h after occlusion, respectively. Importantly, after reperfusion, P_{O_2} levels in both core and penumbra positions increased, but very differently. One hour after reperfusion core P_{O_2} returned to near pre-ischemic levels, 31.6 ± 16.5 mmHg, whilst penumbral P_{O_2} showed only partial recovery to a level of 19.1 ± 6.7 mmHg. So it is demonstrated that the interstitial P_{O_2} levels in penumbra and core are differentially affected during ischemia and reperfusion.

Tissue hypoxia-induced by brain insults plays a critical role in the primary and secondary events leading to cell death after cerebral ischemia (Zauner et al., 2002). Therefore, improving brain tissue oxygenation is a logical and important strategy of stroke treatment to delay the transition of ischemia to infarction (“buying time”). Several experimental studies showed that hyperbaric and normobaric hyperoxia (NBO) was able to impressively reduce the stroke lesion volumes (Miyamoto and Auer, 2000; Flynn and Auer, 2002; Singhal et al., 2002a,b; Günther et al., 2005; Kim and Singhal, 2005), significantly extended the time window for reperfusion, and induced lasting neuroprotection in permanent ischemia (Henninger et al., 2007). Liu et al. (2004) have found that hyperoxic treatment (532 mmHg O_2 for 60 min) significantly increased penumbral P_{O_2} during ischemia, but not in the core. They also found that 722 mmHg normobaric O_2 given during ischemia was able to maintain penumbral interstitial P_{O_2} levels close to the pre-ischemic value while it may cause a two-fold increase in penumbral P_{O_2} level if given during reperfusion (Liu et al., 2006).

OXYGEN TENSION CHANGES IN BRAIN TISSUES DURING HYPERBARIC AND HYPOBARIC OXYGEN ENVIRONMENTS

Hyperbaric oxygen therapy is defined by the Undersea and Hyperbaric Medical Society (UHMS) as a treatment in which a patient intermittently breathes 760 mmHg oxygen under a pressure that is greater than the pressure at sea level [a pressure greater than 1 atmosphere absolute (ATA)] (Calvert et al., 2007). HBO has been shown to be a potent means to increase the oxygen content of blood and has been advocated for the treatment of various ailments, including air embolism, carbon monoxide poisoning, wound healing, and ischemic stroke (Calvert et al., 2007; Nemoto and Betterman, 2007). Some studies showed the increase in arterial oxygen content with increasing inspired oxygen at 1 ATA from 159.6 to 760 mmHg and with 760 mmHg oxygen at 1, 2, and 3 ATA. With each step increase in oxygen from 159.6 to 760 mmHg at 1 ATA and 760 mmHg oxygen at 2 and 3 ATA, arterial oxygen content is increased by 2/100 ml. Thus, by increasing oxygen with

760 mmHg oxygen at 1–3 ATA, arterial oxygen content is increased by 4 ml/100 g/min (Nunn, 1969). The oxygen tension in brain capillary blood was also enhanced by the increased oxygen pressure (to 2.0, 3.0, and 3.5 ATA), but fell down in the venous blood; While, the supplementation of 2% CO_2 to oxygen at 3.5 ATA tremendously increases the mean capillary P_{O_2} and the oxygenation of venous blood (Balenane, 1982). Exposure to 7 ATA O_2 showed two to three-fold increases in oxygen in the cerebral cortex, hippocampus, and the reticular formation compared to air breathing and considerably less than that expected (Torbaty et al., 1976, 1977). Vasoconstriction in response to HBO could be the reason for the blunted increase in brain tissue P_{O_2} during HBO exposure, in addition to the possibility of increased the cerebral metabolic rate of oxygen ($CMRO_2$) associated with increased electrical activity at high oxygen pressures in the range of 7 ATA (Nemoto and Betterman, 2007).

Hyperbaric oxygenation, breathing of 760 mmHg O_2 under hyperbaric conditions, is a potent method to increase the O_2 concentration in tissue with impaired blood supply. Experimental as well as clinical studies have reported a positive effect of HBO therapy. Survival rate has increased under HBO therapy and neurological outcome has improved (Fischer et al., 2010). However, the HBO treatment in cerebral ischemic–anoxic is the proverbial “double-edged sword” because of the dual nature of oxygen in being essential to life and at the same time, it is toxic in excess (Nemoto and Betterman, 2007). It is noted that, in preclinical studies, HBO therapy was effective if administered within 6 h post-stroke after transient middle cerebral artery occlusion and worsened the severity of injury if applied 12 h or later after the stroke (Lou et al., 2004).

Hypobaric hypoxia (HH) is a predisposing environmental condition at high altitude (HA), where although barometric pressure decreases exponentially as altitude is gained, the percentage of each gas component of air is constant up to 12,000 m (Wilson et al., 2009). Therefore, although the proportion of oxygen remains unchanged at 20.93%, increases in altitude result in a lower partial pressure of oxygen in the inspired air. This reduction in the driving gradient on the oxygen cascade can compromise the supply of adequate oxygen to the tissues (Wilson et al., 2009). Compensatory hyperventilation, tachycardia, erythropoietin-induced polycythemia, and increased cerebral blood flow (CBF) can partially maintain cerebral oxygen delivery at HAs (West et al., 2007). However, because the brain is exquisitely sensitive to hypoxia, it is the first organ to be compromised when these mechanisms are inadequate (West, 1996; West et al., 2007). HH is known to cause various neurological clinical syndromes, including high altitude headache (HAH), acute mountain sickness (AMS), and high altitude cerebral edema (HACE), and the genetics, molecular mechanisms, and physiology that underpin them (West et al., 2007).

Some studies indicated that the average venous P_{O_2} in brain tissue is about 30 mmHg at the altitude of about 6000 m, lower than 40 mmHg at the sea level (Boero et al., 1999). It was also found that the HH (28 days, 6000 m) could increase the capillary length per unit volume of tissue (L_v) in the cerebellar granular layer, the caudate nucleus, the globus pallidus, the substantia nigra, the superior colliculus, and the DG, which may accounts for the significant increase of O_2 conductance to neural tissues, and suggested that formation of new capillaries is an important mechanism to restore the O_2 deficit in chronic brain hypoxia and that local rates of energy utilization may

influence angiogenesis in different areas of the brain (Boero et al., 1999). Studies showed that the changes of the CBF depended upon the temporal domains at the HA. Exposure to acute hypoxia is known to cause an immediate increase in CBF, but it is also well known that hypocapnia by itself causes vasoconstriction (Brugniaux et al., 2007). During the acclimatization process, beginning several hours after the start of an altitude exposure and lasting for months (Powell et al., 1998), CBF usually reaches a peak over the first few days followed by a progressive drop toward baseline levels (Wolff, 2000; Wolff et al., 2002). In addition, Dunn et al. (2000) chronically adapted rats to one half an atmosphere of barometric pressure (6000 m) for 27 days and measured the cortical P_{O_2} when animals were breathing normobaric gases. The P_{O_2} in acclimated animals increased rapidly in the first 7 days, then stabilized for the duration of the study. The average P_{O_2} in the acclimated group (from 7 days on) was 62 versus 26 mmHg in the control groups, an increase of 238% (Dunn et al., 2000).

EFFECTS OF OXYGEN TENSION ON THE BEHAVIOR OF NSCs

EFFECTS OF OXYGEN TENSION ON THE BEHAVIOR OF NSCs *IN VITRO*

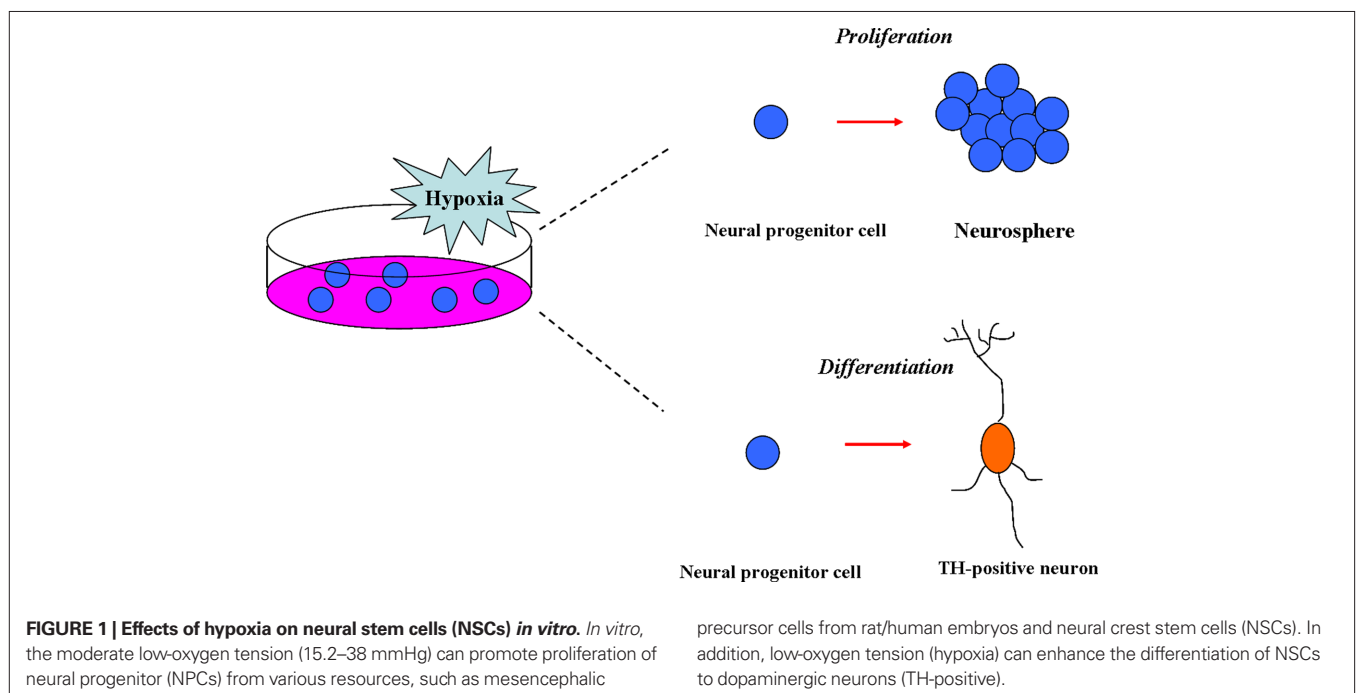
The biological function of oxygen on NSCs *in vitro* was first reported by Studer and Morrison. Studer analyzed mesencephalic precursor cells from rat embryos in embryonic day 12 (E12) in traditional cultures with 152 mmHg O_2 and in lowered O_2 (22.8 ± 15.2 mmHg). Proliferation was promoted and apoptosis was reduced when cells were grown in lowered O_2 , yielding greater numbers of precursors. The differentiation of precursor cells into neurons with specific neurotransmitter phenotypes was also significantly altered. The percentage of neurons of dopaminergic phenotype increased to 56% in lowered O_2 compared with 18% in 152 mmHg O_2 (Studer et al., 2000). Morrison isolated the neural crest stem cells and tested the growth and differentiation potential of NSCs at 38 mmHg O_2 . They also found that reduced oxygen levels can also promote the survival, proliferation, and catecholaminergic differentiation

of CNS stem cells (Morrison et al., 2000). Storch and his colleagues cultured human mesencephalic neural precursor cells from 9- to 12-week-old fetal brain in low-oxygen (22.8 mmHg) and found long-term proliferation of these cells. Moreover, these human NSCs with low-oxygen culture could also give rise to dopamine (DA) neurons (Storch et al., 2001, 2003). Nobutaka, using the NSCs cultured from the ganglionic eminence of fetal ICR mice on embryonic day 15.5, demonstrated that the highest proliferation and the neuronal differentiation of the NSCs were observed in 15.2 mmHg oxygen, and the switching of the neuronal subtype differentiation from GABA-positive to glutamate-positive neurons was observed in lower oxygen conditions (Horie et al., 2008).

Our studies, with the rat embryonic mesencephalon (E13.5) exposed to different oxygen concentrations (152 mmHg O_2 , 76 mmHg O_2 , and 22.8 mmHg O_2) for 3 days, showed that hypoxia, especially 76 mmHg O_2 , promoted the proliferation of NPCs, and hypoxia-inducible factor-1 α (HIF-1 α) was critical in this process (Zhao et al., 2008). Our researches also demonstrated that NSCs cultured in hypoxia (22.8 mmHg O_2) displayed an increase in the percentage of neurons. Especially the percentage of TH-positive neurons differentiated from NSCs in lowered oxygen increased significantly; the DA content in the medium was higher than under normal conditions. HIF-1 α is also involved in the regulation of dopaminergic differentiation of NSCs in lowered oxygen (Zhang et al., 2006).

In summary, the moderate low-oxygen (15.2–38 mmHg) concentration was able to promote the proliferation of NSCs from various resources and enhance the differentiation of NSCs into the TH-positive neurons (Figure 1).

In addition, it should keep in mind that the “real” oxygen levels at cells in the cell culture experiments actually depend on many different factors including the environment, the medium, the metabolism rate of cells and so on. In our studies on the oxygen levels in the



medium with or without cells in the glove box filled with different levels of oxygen from 20.9 to 0%, we found that the oxygen levels in the medium were actually below that in the environment, but could be changed along with the different oxygen levels in the environment. In addition, the oxygen levels in the medium without cells were lower than that in the medium with cells, which indicated that the metabolism of cells could consume the oxygen in the medium. (e.g., In the oxygen levels of 20.9, 11.6, 5.8, 3.0% environments, the oxygen levels were respectively 18.3, 11.0, 5.8, 2.8% in the medium without cells, and 17.8, 10.45, 5.2, 2.75% in the medium with cells; unpublished results).

EFFECT OF OXYGEN TENSION ON THE BEHAVIORS OF NSCs *IN VIVO*

Neural stem cells *in vivo* mainly exist in the SVZ beside the striatum and the DG in the hippocampus of animals. Various stimulations can promote the proliferation and differentiation of NSCs *in vivo*, including physiological stimulations (e.g., physical exercises and learning) and pathological stimulations (e.g., seizures and stroke; Scharfman et al., 2003; Ohab et al., 2006; Scharfman and Gray, 2007; Shetty and Hattiangady, 2007; Bednarczyk et al., 2009; Clelland et al., 2009). The direct relationship of the oxygen concentration with the NSCs can be reflected by the neurogenesis during stroke and in the hyperbaric and hypobaric oxygen environment. So we focus on the above three situations to state the effect of oxygen concentration on proliferation and differentiation of NSCs.

Gu et al. (2000) first discovered the neurogenesis after stroke by *in vivo* Bromodeoxyuridine (5-bromo-2'-deoxyuridine, BrdU) incorporation assay, which is commonly used in the detection of proliferating cells in living tissues. They used the photothrombotic ring stroke model to investigate the cell proliferation process in the ischemically challenged region-at-risk after focal cerebral ischemia in the adult rat brain. The BrdU-positive cells (3–6%) were double-labeled with the neuronspecific marker Map-2 at 7 and 100 days after stroke onset in the region-at-risk. They were distributed randomly in cortical layers II–VI. This study suggests that, as a potential pathway for brain repair, new neurons can be generated in the cerebral cortex of adult rats after sublethal focal cerebral ischemia (Gu et al., 2000). John and his colleagues show that stroke induces neurogenesis from a GFAP-expressing progenitor cell in the SVZ and migration of newly born neurons into a unique neurovascular niche in peri-infarct cortex. Within this neurovascular niche, newly born, immature neurons closely associate with the remodeling vasculature. Neurogenesis and angiogenesis are causally linked through vascular production of stromal-derived factor 1 (SDF1) and angiopoietin 1 (Ang1; Ohab et al., 2006). Furthermore, Pär Thored and Ohab found that the vasculature also plays an important role for long-term striatal neurogenesis after stroke (Ohab et al., 2006; Thored et al., 2007). During several months, neuroblasts migrate close to blood vessels through an area exhibiting early vascular remodeling and persistently increased vessel density (Thored et al., 2007). In addition, new neuroblasts are recruited to an area in the peri-infarct cortex, exhibiting endothelial cell proliferation for the first days after cortical stroke (Ohab et al., 2006). All the above studies showed the significant functions of vascular niche in the processes of neurogenesis after stroke, and implied that the higher oxygen tension around the vessels may be a key factor affecting the neurogenesis induced by stroke.

In addition, it has been found that the HBO treatment can result in the proliferation of BrdU-positive cells and alleviate the myelin damage following hypoxic–ischemic brain damage (HIBD) in neonatal rats (Yu et al., 2006), which indicated that HBO therapy stimulated cells to proliferate in hypoxic–ischemic (HI) neonate rats. Xiao-Li and his colleagues have also found that there were remarkable increases in the proliferation of NSCs in the HBO-treated group, 3, 6, 12, and 24 h after HI, as compared with the HIBD group. The HBO-treated group, 3, 6, and 12 h after HI, performed better in the behavioral test and had less neural loss in the hippocampal CA1 region as compared with the HIBD group. The therapeutic window for effective HBO treatment could be delayed up to 12 h after HIBD, while the effect decreased 24 h after HI (Wang et al., 2008). They proposed that HBO treatment promote stem cells to proliferate, which is correlated with Wnt-3 protein (Wang et al., 2007). In addition, it has been found that the NSCs in neonatal HI rats were able to differentiate and migrate after HBO treatment (Yang et al., 2008). It has also been detected that HBO can up-regulate the differentiated ratio of brain-derived NSCs to neurons (Peng et al., 2007).

Studies also showed that the HH could affect the plasticity of neurons and neurogenesis of animals. It was found that there were impairment of spatial memory and a significant decrease in dendritic arborization and spine number along with increased number of damaged neurons after 3 and 7 days of HH (6100 m) exposure, but after 21 days of HH exposure the improvements of memory and structure were noted (Maiti et al., 2008). However, intermittent hypoxia exposure (4 h/day) to neonatal mice at 2000 m for 3 or 4 weeks increased p-CREB, LTP, and synapses of hippocampus, and enhanced mice spatial learning and memory (Zhang et al., 2005). We also made investigative effort to find out whether intermittent hypoxia affects neurogenesis in the adult rat brain by examining the newly divided cells in the SVZ and DG. Our studies showed that the BrdU-labeled cells in the SVZ and DG increased after 3000 and 5000 m (4 h/day for 2 weeks) intermittent hypoxia. The number of BrdU-labeled cells in the SVZ returned to normal level 4 weeks following intermittent hypoxia. However, the BrdU-labeled cells in the DG had a two-fold increase 4 weeks subsequent to intermittent hypoxia. We conclude that intermittent hypoxia facilitates the proliferation of NSCs *in situ*, and that the newly divided cells in the SVZ and DG react differently to hypoxia (Zhu et al., 2005a).

In summary, the three situations including stroke, HBO, and HH are all able to promote the neurogenesis *in vivo*. It is interesting to note that the common consequences caused by all the above three situations are the changes of the levels of oxygen concentration *in vivo*, including up-regulation and down-regulation. So we conclude that it is the changes of oxygen concentration, both including the increase or decrease of oxygen concentration, which induce the promotion of neurogenesis *in vivo* (Figures 2 and 3).

THE POSSIBLE MOLECULARS INVOLVED IN REGULATING NEUROGENESIS

Hypoxia exists not only in the brain tissue, such as cortex, striatum, hippocampus, thalamus etc. (Ndubizu and LaManna, 2007), but also in the developing embryos, which is known to regulate the proliferation and differentiation of NSCs *in vitro* and *in vivo*

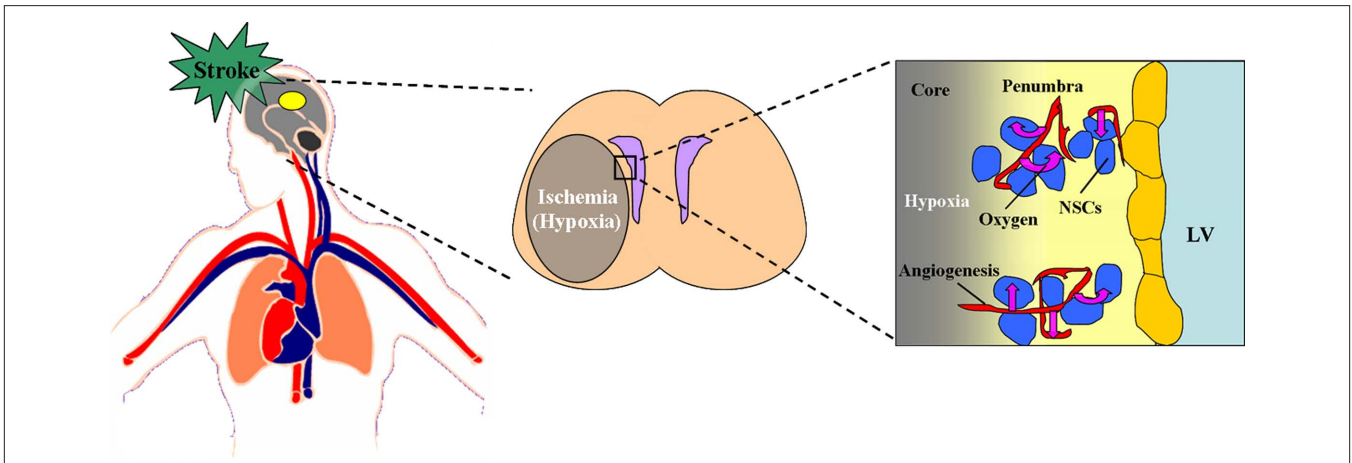


FIGURE 2 | Effect of stroke on the oxygen niche around NSCs *in vivo*. During the stroke, the thrombus block the blood and oxygen supply to the pathological region of brain, which cause the ischemia and hypoxia in the core and penumbra. In the penumbra, the angiogenesis and neurogenesis take place. Within this neurovascular niche, newly born, immature neurons closely associate with the

remodeling vasculature. The oxygen tension around the remodeling vasculature is much higher than the other ischemic part, which implies that the higher oxygen tension around the vessels may be a key factor affecting the neurogenesis induced by stroke. The figure of circulatory system is referenced from the webpage (http://heart.wehealny.org/heart_tour/about.html).

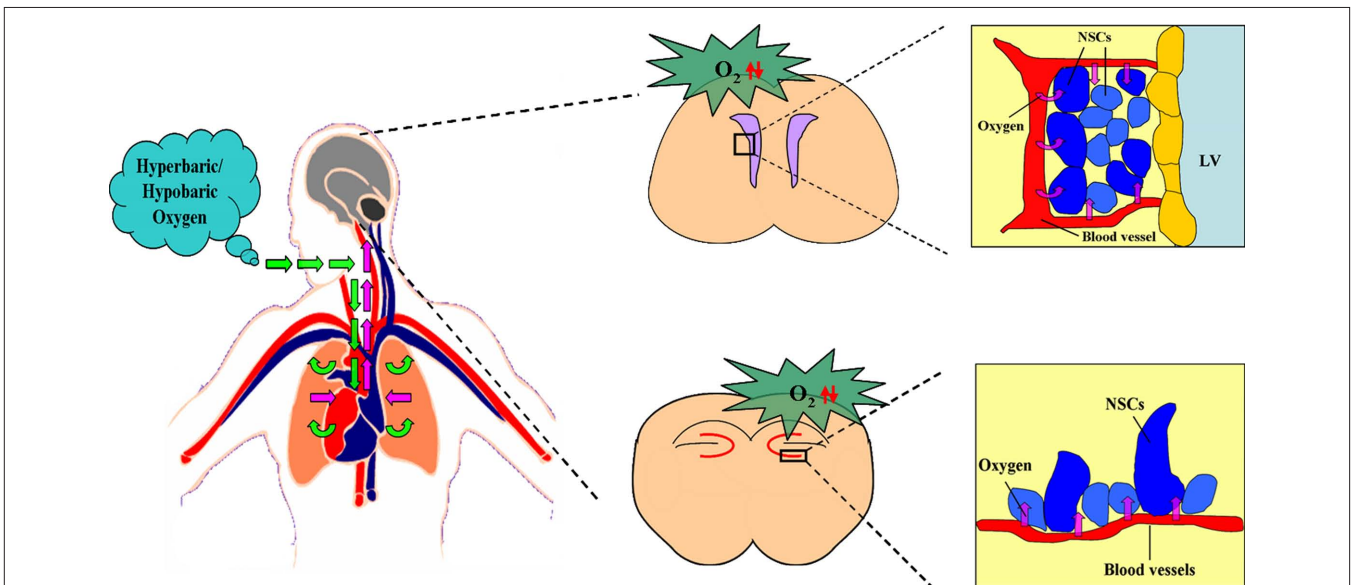


FIGURE 3 | Effect of hyperbaric/hypobaric oxygen on the oxygen niche around NSCs *in vivo*. Hyperbaric/hypobaric oxygen enhance/reduce the oxygen levels in pulmonary alveoli through respiratory system, which causes the alteration of the oxygen concentration in arterial blood, and changes the oxygen supply to the various

areas of brain, including SVZ and DG. This lead the increase/decrease of oxygen tension in blood capillaries of SVZ and DG, which determines the P_{O_2} around the neural stem cells (NSCs) in the above two regions. The figure of circulatory system is referenced from the webpage (http://heart.wehealny.org/heart_tour/about.html).

(Zhu et al., 2005b). Many of the cellular responses to hypoxia are mediated through changes in gene expression. The transcription factors primarily responsible for these changes are the HIFs, the biological function of which has been reviewed elsewhere (Keith and Simon, 2007; Panchision, 2009). Recent studies have identified new molecular mechanisms which modify the behaviors and functions of NSCs in lower oxygen levels. Here, we will focus on the Notch1, Bone morphogenetic protein (BMP), and Wnt signaling pathway to understand the regulation of cellular behaviors and functions of NSCs during hypoxic environment.

NOTCH PATHWAY

Notch is a transmembrane receptor for the ligands Delta and Jagged; ligand binding activates the cleavage of Notch and the transport of the notch intracellular domain (NICD) to the nucleus to regulate transcription of target genes (Gordon et al., 2008). Notch signaling acts as a stem cell self-renewal and antineurogenic signal during CNS development (Corbin et al., 2008). Gustafsson et al. (2005) reported that hypoxia blocked the differentiation of myogenic satellite cells, a myogenic cell line (C2C12), and primary NSCs in a Notch-dependent manner.

It was found that hypoxia activates Notch-responsive promoters and increases expression of Notch direct downstream genes. The NICD interacts with HIF-1 α , a global regulator of oxygen homeostasis, and HIF-1 α is recruited to Notch-responsive promoters upon Notch activation under hypoxic conditions (Gustafsson et al., 2005). Diez et al. (2007) also identified the reduced oxygen levels lead to activation of the Dll4-Notch-Hey2 signaling cascade and subsequent repression of COUP-TFII in endothelial progenitor cells. Cecilia showed that Notch signaling is required to convert the hypoxic stimulus into epithelial-mesenchymal transition (EMT), increased motility, and invasiveness. Inhibition of Notch signaling abrogated hypoxia-induced EMT and invasion. Conversely, activated form of Notch could substitute for hypoxia to induce these processes (Sahlgren et al., 2008).

It has also been found that the activation of HIF-1 by short-term NiCl₂ treatments (a condition of chemical hypoxia) dramatically increased APH-1A (a component of γ -secretase complex) mRNA and protein expression, indicative of an increase in γ -secretase activity. The cellular concentration of NICD was also increased after hypoxia treatment (Wang et al., 2006).

In addition, it has been demonstrated that an additional level of complexity in this cross-talk: factor-inhibiting HIF-1 (FIH-1) regulates not only HIF activity, but also the Notch signaling output and, in addition, plays a role in how Notch signaling modulates the hypoxic response (Zheng et al., 2008). They showed that FIH-1 hydroxylates Notch ICD at two residues (N¹⁹⁴⁵ and N²⁰¹²) that are critical for the function of Notch ICD as a transactivator within cells and during neurogenesis and myogenesis *in vivo*. FIH-1 negatively regulates Notch activity and accelerates myogenic differentiation (Zheng et al., 2008).

BMP PATHWAY

Bone morphogenetic proteins are members of the TGF- β superfamily. These secreted ligands bind to receptor complexes that catalyze the phosphorylation and activation of the canonical SMAD proteins 1, 5, and 8, which complex with Smad4 and translocate to the nucleus to regulate the transcription of target genes (Nohe et al., 2004). BMPs are critical regulators of dorsoventral patterning during development and are well-characterized inducers of CNS stem cell differentiation, astroglial fate, mitotic arrest, and apoptosis. In contrast, the endogenously secreted BMP antagonist, noggin, limits glial differentiation, and redirects normal postnatal NSCs to generate neurons (Panchision, 2009).

Pistollato indicated that lowered oxygen tension repressed BMP signaling and subsequent glial differentiation of CNS precursor cells, while a higher oxygen tension promoted BMP signaling. The underlying mechanism may be caused by the repression of Smad1/5/8, a key step in BMP signal transduction, in low-oxygen tension (Pistollato et al., 2007). It has also been found that the BMP signaling was actively repressed by hypoxia with the high-grade glioma (HGG) precursors which generated endogenous BMP signaling. An acute increase in oxygen tension led to Smad activation within 30 min, even in the absence of exogenous BMP treatment. Furthermore, Pistollato et al. (2009) detected that silencing of HIF-1 α led to Smad activation even under hypoxic conditions,

indicating that HIF1 α was required for BMP repression. Conversely, BMP activation at high oxygen tension led to reciprocal degradation of HIF1 α ; this BMP-induced degradation was inhibited in low-oxygen.

WNT/ β -CATENIN PATHWAY

β -Catenin is the key effector molecule in canonical Wnt signaling pathway. The binding of Wnt proteins to the seven-membrane-spanning frizzled receptors (Frz) the stabilization and accumulation of cytosolic β -catenin. The increased levels of β -catenin in the cytosol result in its nuclear translocation. In the nucleus, β -catenin interacts with members of the lymphoid enhancer binding factor/T cell-specific factor (LEF/TCF) family of transcription factors and activates expression of target genes such as c-myc and cyclins (Willert and Nusse, 1998; Cui et al., 2010).

During the mammalian embryonic development, the Wnt/ β -catenin signaling pathway regulates embryonic NSC proliferation and fate determination (Chenn and Walsh, 2002; Hirabayashi et al., 2004). Canonical Wnt/ β -catenin signaling pathway also plays a crucial role in neurogenesis in adult mammalian CNS (Lie et al., 2005).

Jolly and his colleagues found that hypoxia activated Wnt/ β -catenin signaling in mouse embryonic cells and HIF-1 (HIF-1 α /ARNT complex) mediated hypoxia-induced Wnt signaling in embryonic cells. This regulation extended to primary cells, including isolated NSCs, and was not observed in differentiated cells. *In vivo*, *Hif-1 α* deletion impaired hippocampal Wnt-dependent processes, including NSC proliferation and differentiation. This decline correlated with reduced Wnt/ β -catenin signaling in the SGZ (Jolly et al., 2010). Cui has also found that hypoxia could enhance the proliferation of hippocampal NSCs and β -catenin contributed to this action (Cui et al., 2010). Therefore, both of the above studies implied that O₂ may have a direct role in stem cell regulation through HIF-1 α modulation of Wnt/ β -catenin signaling.

In addition, Kaidi et al. (2007) have found that hypoxia was able to block colorectal tumor cell proliferation. Kaidi et al. (2007) reported that hypoxia inhibited the proliferation of colon carcinoma cells in a β -catenin-dependent manner. Hypoxic treatment resulted in increased cell-cycle arrest and down-regulated expression of the Wnt/ β -catenin target c-Myc, a potent cell-cycle regulator. Hypoxic inhibition of Wnt/ β -catenin signaling was mediated by physical interaction of HIF-1 α with β -catenin, resulting in reduced formation of β -catenin-TCF-4 complexes (Jolly et al., 2009).

CONCLUSION

Studies reviewed here provide the data of oxygen concentration in cerebral tissue during embryonic and adult neurogenesis, and the cerebral oxygen level changes during cerebral disease and in hypobaric/HBO. The role of oxygen in the behaviors of NSCs is also reviewed through the *in vivo* and *in vitro* experimental evidences (Tables 1 and 2).

The significant function of oxygen in the differentiation and proliferation of NSCs raises the possibilities of amplifying NSCs *in vitro* for stem cell treatments by providing hypoxic niche around the cells. In addition, it is also possible to induce the neurogenesis *in vivo* by the modification of the oxygen environment around the

Table 1 | Oxygen levels in brain during physiological/pathological state and specific environment *in vivo*.

<i>In vivo</i>				
PHYSIOLOGICAL STATE	PERIOD	REGION OF BRAIN	P _{o2} VALUE (mmHg)	CITATION
	Embryo	Neural tube of embryo	<7.6	Lord et al. (1993)
		Folding neural tube of mouse embryo at embryonic day 8.5–9.0 (E8.5–9.0); neural tubes of mouse embryo at E9.5–11.5; cranial flexure, myelencephalon, and choroid plexi of mouse embryo at E12.5	<7.6	Lee et al. (2001)
	Adult	Dentate gyrus	6–8	Zhang et al. (2010)
		Lateral ventricles of adult rat	42–48	Zhang et al. (2010)
		White matter of frontal lobes of adult human	25–30	Sarrafzadeh et al. (1998)
		Striatum of adult rats	33.4 ± 6.0	Liu et al. (2004)
PATHOLOGICAL STATE	INSULTS	STATUS	P _{o2} VALUE (mmHg)	CITATION
	Stroke	Ischemic penumbra of adult rat 1 h after MCAO	10.7 ± 7.8	Liu et al. (2004)
		Ischemic core of adult rat 1 h after stroke MCAO	1.2 ± 0.7	Liu et al. (2004)
		Penumbra of adult rat 1 h after reperfusion	19.1 ± 6.7	Liu et al. (2004)
		Core of adult rat 1 h after reperfusion	31.6 ± 16.5	Liu et al. (2004)
		Penumbra of adult rat breathing 30, 70, 95, 100% oxygen 90 min after MCAO	12.3; 17.4; 34.1; 38.2	Liu et al. (2006)
	Trauma	Brain tissue of survivors	N.C. (Higher)	van den Brink et al. (2000)
		Brain tissue at risk of death	<15 for longer than 30 min	van den Brink et al. (2000)
		Brain tissue at risk of death	<10 for 10 min	van den Brink et al. (2000)
		A greater risk for dying	<6	Valadka et al. (1998)
SPECIFIC ENVIRONMENT	TREATMENT	OXYGEN ENVIRONMENT (ALTITUDE)	P _{o2} VALUE (mmHg)	CITATION
	HBO	N.C.	N.C.	N.C.
	HH	Brain tissue of adult mice at the sea level	40	Boero et al. (1999)
		Brain tissue of adult mice at the altitude of 6000 m	30	Boero et al. (1999)
		Front cortex of adult rat acclimated at the altitude of 6000 m from the 7 to 27th-day when animals were breathing normobaric gases	62	Dunn et al. (2000)

HBO, hyperbaric oxygen; HH, hypobaric hypoxia.

body, which provides us a novel idea to promote the ability of learning and memory because of the involvement of neurogenesis in the process of cognition (Kempermann and Gage, 2002), and reminds

us a new method for treating some mental illness because of the links between adult neurogenesis and mental disorders, such as Alzheimer's Disease and schizophrenia (DeCarolis and Eisch, 2010).

Table 2 | Neural stem cells behaviors regulated by hypoxia *in vitro*.

<i>In vitro</i>				
SURVIVAL	SOURCE OF NSCs	PROMOTION ±	P _{o2} VALUE (mmHg)	CITATION
	E14.5 rat neural crest stem cells	+	38	Morrison et al. (2000)
	E12 rat mesencephalon	+	22.8 ± 15.2	Studer et al. (2000)
	Fetal human brain	–	76	Stantilli et al. (2010)
	ESC-derived NSCs	+	30.4	Clarke and Kooy (2009)
	P0 mice hippocampus	+	38	Cui et al. (2010)
PROLIFERATION	SOURCE OF NSCs	PROMOTION ±	P _{o2} VALUE (mmHg)	CITATION
	E12 rat mesencephalon	+	22.8 ± 15.2	Studer et al. (2000)
	E14.5 rat neural crest stem cells	+	38	Morrison et al. (2000)
	E14.5 rat or E14.5 mouse mesencephalon	+	22.8	Storch et al. (2001, 2003)
	E15.5 mice ganglionic eminence	+	15.2	Horie et al. (2008)
	E13.5 mouse mesencephalon	+	76	Zhao et al. (2008)
	Fetal human brain	+	19	Stantilli et al. (2010)
	Fetal human brain	+	38	Stantilli et al. (2010)
	P0 mice hippocampus	+	38	Cui et al. (2010)
DIFFERENTIATION	DIRECTION	PROMOTION ±	P _{o2} VALUE (mmHg)	CITATION
	Dopaminergic neurons	+	22.8 ± 15.2	Studer et al. (2000), Storch et al. (2001, 2003)
	Catecholaminergic neurons	+	38	Morrison et al. (2000)
	Switching from GABA-positive to glutamate-positive neurons	+	15.2	Horie et al. (2008)
	TH-positive neurons	+	22.8	Zhang et al. (2006)
	GABAergic and slightly of glutamatergic neurons; oligodendrocytes	+	19	Stantilli et al. (2010)

+ Promotion; – inhibition.

Because of the heavy oxygen consumption of brain and the low-oxygen level inside cerebral tissue, maintaining the narrow ranges of tissue P_{o2} may be beneficial to normal brain function. Higher or lower levels of tissue P_{o2} may affect normal chemical production, possibly leading to brain cell damage. However, the physiological mechanism of oxygen sensing and control remains largely unknown (Masamoto and Tanishita, 2009). Novel knowledge and innovative techniques are expected to

allow formation of a complete and dynamic picture of oxygen transport and metabolism during normal and pathological brain activities.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Basic Research Program of China, No. 2006CB504100; The Natural Science Foundation of China, No. 308311605 and 90919052.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 26 January 2011; accepted: 23 March 2011; published online: 04 April 2011.

Citation: Zhang K, Zhu L and Fan M (2011) Oxygen, a key factor regulating cell behavior during neurogenesis and cerebral diseases. *Front. Mol. Neurosci.* 4:5. doi: 10.3389/fnmol.2011.00005

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