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Brain preconditioning and obstructive sleep apnea syndrome

Anna Brzecka

Department of Lung Diseases, University of Medicine in Wrocław,
105 Grabiszyńska St., 53-439 Wrocław, Poland, Email: aniabrz@box43.pl

Review

Abstract. Intermittent hypoxia stimulates the development of adaptive responses, called preconditioning. This process is partially mediated by genetic remodeling, via hypoxia inducible factor (HIF), which induces long-term adaptation processes and is responsible for the increase of levels of vascular endothelial growth factor (VEGF), erythropoietin (Epo), atrial natriuretic peptide (ANP), and nitric oxide (NO). The synthesis of brain-derived neurotrophic factor (BDNF) participates in the control of neural plasticity after hypoxia. The mechanisms of neuroprotection against hypoxia may be related to vascular adjustments and to central neurogenic neuroprotection. Some of the factors known to be involved in the development of the mechanism of neuroprotection are also present in the responses to repetitive apneas that occur during sleep in patients with obstructive sleep apnea (OSA) syndrome, who are frequently exposed to severe sleep hypoxemia. It appears that OSA syndrome represents a clinical example of preconditioning and the development of adaptive responses to intermittent hypoxia.

Key words: preconditioning, neuroprotection, plasticity, hypoxia, sleep apnea

INTRODUCTION

The central nervous system is particularly vulnerable to hypoxic conditions; this is due to high-energy requirements compared to the low energy reserves (Hossmann 1999). Long-term exposure to severe hypoxia causes both immediate and delayed functional and metabolic disturbances and can progress to cell injury and deterioration (Ceretelli 1992). However, short-term exposure – as occurs in conditions of repeated and transient reductions in oxygen tension, called intermittent hypoxia – may initiate adaptive responses counterbalancing the effects of oxygen deprivation (Clanton and Klawitter 2001). The development of the spectrum of adaptive mechanisms protecting nerve cells from oxygen deprivation in the course of intermittent hypoxia has been called preconditioning; the idea of preconditioning arose in the cardiac literature (Murry et al. 1986). Subsequently, preconditioning has been found in multiple organs, including the central nervous system (Clanton and Klawitter 2001, Dirnagl et al. 2003, Vanden Hoek 2002). It has been shown in numerous experimental models of cerebral ischemia that brief episodes of ischemia make the brain more resistant to following longer ischemic events (Bergeron et al. 2000, Kirino 2002, Schaller and Graf 2002, Weih et al. 2001). Neurons can be preconditioned by various mechanisms to resist hypoxia, ischemic tolerance can be observed in different phases, and several mediators are implicated in preconditioning (Sato et al. 2000, Schaller and Graf 2002, Weih et al. 2001, Yellon et al. 1998).

GENETIC AND HUMORAL RESPONSES TO INTERMITTENT HYPOXIA

Delayed and long-lasting neuroprotection against hypoxia may involve genetic remodeling with expression or repression of multiple genes (Golanov and Zhou 2003, Weih et al. 2001). The adaptations to hypoxia are mediated by hypoxia-inducible factor-1 (HIF-1) (Zhou et al. 2003). HIF-1 is a heterodimeric factor, composed of HIF-1α and HIF-1ß protein subunits, that senses decreased oxygen availability and – after binding to promoter/enhancer elements – responds with enhanced transcription of classic hypoxia-inducible target genes (Sharp et al. 2001, Zhou et al. 2003). The genes stimulated by HIF-1 are involved in angiogenesis, erythropoiesis, and energy metabolism, thus inducing the long-term adaptation processes (Sharp et al. 2001, Yamakawa et al. 2003, Zhou et al. 2003). HIF-1 upregulates the levels of erythropoietin (Epo) (Sanchez-Elsner et al. 2004), vascular endothelial growth factor (VEGF)(Yamakawa et al. 2003), atrial natriuretic peptide (ANP) (Chun et al. 2003), nitric oxide (NO) synthase (Jung et al. 2000), glucose transport proteins (Brooks et al. 1991), and glycolytic enzymes (Sharp et al. 2001).

Epo is a hydrophobic sialoglycoproteic, hematopoietic growth factor, produced in response to hypoxia by the kidney, liver, and spleen (Buemi et al. 2002, 2003, Eid and Brines 2002). The system of Epo and its receptors – present in neurons, glial cells and brain capillary endothelial cells – is upregulated in conditions of both cerebral ischemia and hypoxia (Kalialis and Olsen 2003, Siren et al. 2001a). Epo has neurotrophic and multiple neuroprotective effects and is considered a cellular survival factor in neurons (Juul 2002, Sinor and Greenberg 2000, Siren et al. 2001b). The mechanisms by which Epo produces neuroprotection include decreased glutamate toxicity, inhibition of apoptosis, reduced inflammation, antioxidant effects, and stimulation of angiogenesis (Brines et al. 2000, Celik et al. 2002, Digicaylioglu and Lipton 2001, Grimm et al. 2002, Juul 2002, Olsen 2003, Siren et al. 2001a). Increased Epo levels in response to hypoxia prevent light-induced retinal degeneration (Grimm et al. 2002). In animal models exogenous Epo may cause reduction of cerebral infarct after reversible middle cerebral artery occlusion (Brines et al. 2000, Siren et al. 2001a). In cultured rat cortical neurons Epo reduces neuronal cell death from hypoxia with glucose deprivation (Sinor and Greenberg 2000).

VEGF is a hypoxia-sensitive glycoprotein stimulating the growth of new capillary vessels (Jurkovicova et al. 2003, Lavie et al. 2002). In severely hypoxic patients serum levels of VEGF are elevated in the relation to the degree of oxygen desaturation (Schultz et al. 2002, Teramoto et al. 2003b). Systemic hypoxia also upregulates VEGF in the brain (Xu and Severinghaus 1998). The presence of VEGF has been shown in the brain after moderate ischemia-reperfusion injury (Mu et al. 2003). VEGF may play a role in the regulation of oxygen tissue delivery (Gozal et al. 2002). In the models of hypoxic preconditioning, activation of VEGF has neuroprotective properties (Bernaudin et al. 2002, Mu et al. 2003, Wick et al. 2002).

Plasma ANP levels increase during hypoxia. Protection conveyed by ANP may involve the attenuated activation of pro-inflammatory transcription factors and the reduced expression of tumor necrosis-factor-α (Kiemer et al. 2000). ANP has been found to exhibit a cytoprotective anti-ischemic (preconditioning-like) function within the heart and coronary circulation (D'Souza et al. 2004). ANP is present in cerebral cortex and its action is mediated *via* cGMP production (Wiggins et al. 2003). ANP may contribute to neuroprotection, as has been shown in animal studies (Wiggins et al. 2003).

Endothelial NO, i.e., endothelium-dependent-relaxation-factor, synthesized at the intravascular/extravascular interface and released in hypoxic conditions, has vasodilating properties before it is broken down into nitrates (Remsburg et al. 1999, Thomas et al. 2001) and may be implicated in the induction of preconditioning (Lebuffe et al. 2003). NO enhances tissue cellular respiration; gradients of NO, radiating from the vessel, inhibit mitochondrial respiration in locations of high partial oxygen pressure, close to the vessel, thus preserving oxygen gradients for mitochondria at greater distances (Thomas et al. 2001). Hypoxia upregulates endothelial and neuronal isoforms of NO synthase (Javeshghani et al. 2000). The results of the animal studies show that although NO derived from the neuronal isoform of NO synthase promotes an inflammatory response in the cerebrovascular microcirculation after short-term episodic hypoxia, NO produced by endothelial isoforms of NO synthase blunts the extent of this response and exerts neuroprotective effects (Altay et al. 2004). It has been shown in experimental studies that preconditioning leads to an increase of reactive oxygen species production in cultures of cardiomyocytes (Vanden Hoek et al. 1998). Reactive oxygen species can trigger preconditioning by causing activation of the ATP channel, which then induces generation of NO (Lebuffe et al. 2003).

It has been recently shown that intermittent hypoxia increases brain-derived neurotrophic factor (BDNF) synthesis (Baker-Herman et al. 2004). This neurotrophin is known to be involved in the control of neural plasticity during hypoxia and recovery from hypoxic injury (Scheepens et al. 2003) and to be able to prevent and/or reduce neuronal death induced by hypoxic-ischemic events (Aloe and Iannitelli 2001). The results of animal studies have shown that BDNF has potent neuroprotective actions, especially in the developing brain (Cheng et al. 1997). BDNF induces the reduction of the proapoptotic protein and counter-regulates the antiapoptotic protein thus markedly reducing infarct volume and improving neurological outcome in a model of temporary cerebral ischemia in rats (Schäbitz et al. 2000). It has been also shown in the models of neonatal hypoxic-ischemic brain injury that BDNF inhibits apoptosis and exhibits marked neuroprotective effects (Han and Holtzman 2000, Han et al. 2000).

CEREBROVASCULAR REGULATORY SYSTEM AND CENTRAL NEUROGENIC NEUROPROTECTION

Powerful cerebrovascular regulatory systems protect the brain against hypoxia, assuring an increase of blood flow to compensate for the reduced arterial oxygen content (Hossmann 1999). In clinical settings and in models of intermittent hypoxia there is an overall stimulation of the sympathetic outflow, resulting in systemic hypertension (Fletcher 2000, Narkiewicz et al. 1999). Epinephrine can have secondary effects on multiple metabolic pathways (Navegantes et al. 2000). This system is so efficient that during respiratory hypoxia brain metabolism is little disturbed as long as cardiac function does not fail (Hossmann 1999). Only with declining blood pressure does cerebral blood flow decline, and brain energy metabolism rapidly collapses (Hossmann 1999).

Reis and colleagues formulated the principle of central neurogenic neuroprotection (Reis et al. 1997). Central neurogenic neuroprotection constitutes an independent system, designed to protect the brain from ischemia (Golanov and Zhou 2003, Golanov et al. 1998, Reis et al. 1997). Conditioned central neurogenic neuroprotection is mediated by the intrinsic neurons of the cerebellar fastigial nucleus (Golanov and Zhou 2003, Golanov et al. 1998, Reis et al. 1997). Central neurogenic neuroprotection exerts long-lasting effects and is associated with reduced excitability of cortical neurons and reduced immunoreactivity of cerebral microvessels (Reis et al. 1997). In experimental studies electrical stimulation of the cerebellar fastigial nucleus for 1 h prior to transient four-vessel occlusion in anesthetized rats salvaged 57% of the CA1 zone of dorsal hippocampus from delayed neuronal death (Golanov et al. 1998); 1-hour of stimulation protected the brain for up to three weeks (Golanov and Zhou

2003). Electrical stimulation of the cerebellar fastigial nucleus for 1 h, 48 h before occlusion of the middle cerebral artery reduced infarct volumes by 45% by decreasing cellular death in the ischemic penumbra (Galea et al. 1998). The stimulation of the other brain structures such as subthalamic cerebrovasodilator area and dorsal periaqueductal gray matter also produces long-lasting brain salvage (Golanov and Zhou 2003). It has been also shown that the excitation of intrinsic neuronal pathways represented in fastigial nucleus is not restricted to focal ischemia, but it also protects the brain against global ischemia (Golanov et al. 1998, Reis et al. 1997). After global cerebral ischemia, ischemic tolerance may protect up to 90% of hippocampal CA1 neurons (Weih et al. 2001).

INTERMITTENT HYPOXIA IN OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstructive sleep apnea (OSA) syndrome is a common, although often unrecognized and undiagnosed illness, estimated to occur in about 5% of adults (Young et al. 2001). In OSA syndrome the upper airway completely or partially collapses despite respiratory effort. As a consequence negative intrathoracic pressure with increased cardiac preload develops and impaired oxygenation occurs. Arterial oxygen saturation during OSA episodes drops usually by several percent, but sometimes to extremely low levels. Increasing respiratory effort in association with hypoxia or hypercapnia constitute the stimulus to arousal that results in the ending of the apnea episode (Gleeson et al. 1990). The episodes of upper airway collapse repeat frequently – from several to as many as 100 times per hour of sleep. Frequent partial arousals occur throughout sleep, leading to sleep fragmentation and sleep deprivation. The main complaints of OSA patients are associated with excessive daytime sleepiness (Whyte et al. 1989). The most important cardiovascular consequences of OSA are related to hemodynamic changes and repetitive nocturnal hypoxemia during sleep (Parati et al. 2002). Sleep-related breathing disorder may contribute to stroke (Mohsenin 2001). However, most patients with OSA do not develop cerebrovascular impairment, even in the presence of severe nocturnal oxygen desaturations.

Some of the substances involved in the preconditioning have been studied in OSA patients, although the consequences of intermittent hypoxia on brain oxygenation and function remain largely unexplored.

In patients with OSA syndrome Epo levels are higher than in normal subjects (Hu et al. 2002). For example in the study of Cahan and coauthors (1992) OSA patients had Epo levels of 45 mU/ml compared with normal subject's levels of 17 mU/ml. In addition to its neuroprotective action, the influence of Epo on erythropoiesis may be beneficial in OSA patients, exposed to repetitive profound hypoxia, as increased red cell mass may increase tissue oxygen delivery.

Due to nocturnal hypoxemia VEGF concentrations during sleep are significantly higher in OSA patients than in normal subjects (Lavie et al. 2002, Teramoto et al. 2003b). In severely hypoxic patients with OSA the elevated serum levels of VEGF are related to the degree of nocturnal oxygen desaturation (Schultz et al. 2002). Additionally, it has been found that in patients in whom nocturnal hypoxia improves after the current standard treatment for OSA – continuous positive airway pressure (CPAP), VEGF concentrations decrease (Lavie et al. 2002). Increased VEGF levels in OSA patients may contribute to the long-term adaptation to recurrent nocturnal hypoxia and thus may counterbalance the emergence of OSA-related cardiovascular disease (Lavie et al. 2002, Schultz et al. 2002).

The levels of ANP are increased in OSA patients, even twofold (Parati et al. 2002). This may be due to increased cardiac preload and atrial stretch during apnea episodes (Parati et al. 2002). It has been found in patients with chronic obstructive pulmonary disease that ANP levels are increased in pulmonary hypertension and that ANP may both selectively vasodilate pulmonary vessels and inhibit pulmonary vascular remodeling (Rogers et al. 1994). This action of ANP may also be beneficial in hypoxic OSA patients, preventing the development of pulmonary hypertension.

Both the synthesis and breakdown of NO are critically dependent on the presence of oxygen (Schulz et al. 2000). Thus, the systemic production and plasma level of this important vasodilating gas is impaired in OSA patients (Lavie 2003, Parati et al. 2002, Teramoto et al. 2003a). The levels of NO are reduced in OSA patients, sometimes to levels of half those seen in normal subjects. NO levels correlate negatively with the severity of hypoxemia (Remsburg et al. 1999). However, the mechanisms of hypoxic vasodilatation related to NO appear to be tissue specific and are not uniform across the vascular bed (Halliwill 2003), so

the exact role of nitric oxide in brain preconditioning in OSA patients remains unexplored.

Increased BDNF synthesis is involved in the generation of hypoxia-induced plasticity in the central nervous system (Mitchell et al. 2001). Plasticity in the central neural control of breathing induced by intermittent hypoxia can be measured as long-term facilitation (LTF) of phrenic motor output (Mitchell et al. 2001). LTF is elicited uniquely by intermittent, but not by sustained hypoxia (Baker and Mitchell 2000). This central neural mechanism is associated with increased BDNF synthesis (Mitchel et al. 2001). OSA patients, but not normal control subjects, exhibit ventilatory LTF when awake (McNamara et al. 1995). This phenomenon disappears during the CPAP treatment that abolishes the episodes of arterial oxygen desaturation during sleep (Tun et al. 2000). The specific relevance of enhanced phrenic LTF following intermittent hypoxia in OSA patients is not currently known, but in hypoxic conditions LTF may beneficially augment respiratory function (Baker-Herman et al. 2004).

Hypoxemia (with concomitant hypercapnia) developing during apnea episode results in chemoreflex activation with consequent increases in sympathetic vasoconstrictor traffic to peripheral blood vessels (Somers et al. 1995). This reflex response results in the increased levels of circulating catecholamines and increases in blood pressure (Somers et al. 1995). Cerebral blood flow velocity measured by transcranial Doppler sonography increases during obstructive apnea and decreases after apnea termination concomitant with changes in arterial pressure (Franklin 2002). This may prevent nocturnal cerebral ischemia, which could develop in the state of hypoxemia with low cerebral blood flow and low arterial pressure.

The phenomenon of central neurogenic neuroprotection has not been studied in OSA patients.

CONCLUSIONS

Patients with OSA syndrome, who are nightly exposed to intermittent hypoxia, exhibit a wide variety of autonomic, hemodynamic, humoral and neuroendocrine responses (Lanfranchi and Somers 2001). The mechanisms of preconditioning described here protecting the brain against hypoxia may only partially explain the phenomenon of sometimes well-tolerated episodes of extreme hypoxia that may occur in OSA patients and not lead to evident brain injury. OSA syndrome represents a clinical situation where, despite hundreds of events of severe arterial oxygen desaturation occurring every night, ischemic tolerance of central nervous system allows the brain to avoid immediate injury and enables the survival of affected patients. However, the interaction of the above-mentioned factors related to preconditioning has not been extensively studied and their role in adaptation of the brain to repetitive hypoxia still needs further study.

REFERENCES

Aloe L, Iannitelli A (2001) Neurotrophic factors and brain damage in hypoxic-ischemic encephalopathy: a role of nerve growth factor? (in Italian). Ann Ist Super Sanita 37: 573–580.

Altay T, Gonzales ER, Park TS, Gidday JM (2004) Cerebrovascular inflammation after brief episodic hypoxia: modulation by neuronal and endothelial nitric oxide synthase. J Appl Physiol 96: 1223–1230.

Baker TL, Mitchell GS (2000) Episodic but not continuous hypoxia elicits long-term facilitation of phrenic motor output in rats. J Physiol (Lond) 15: 215–219.

Baker-Herman TL, Fuller DD, Bavis RW, Zabka AG, Golder FJ, Doperalski NJ, Johnson RA, Watters JJ, Mitchell GS (2004) BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. Nat Neurosci 7: 48–55.

Bergeron M, Gidday JM, Yu AY, Semenza GL, Ferriero DM, Sharp FR (2000) Role of hypoxia-inducible factor-1 in hypoxia-induced ischemic tolerance in neonatal rat brain. Ann Neurol 48: 285–296.

Bernaudin M, Nedelec AS, Divoux D, MacKenzie ET, Petit E, Schumann-Bard P (2002) Normobaric hypoxia induces tolerance to focal permanent cerebral ischemia in association with an increased expression of hypoxia-inducible factor-1 and its target genes, erythropoietin and VEGF, in the adult mouse brain. J Cereb Blood Flow Metab 22: 393–403.

Brines ML, Ghezzi P, Keenan S, Agnello D, de Lanerolle NC, Cerami C, Itri LM, Cerami A (2000) Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. Proc Natl Acad Sci U S A 97: 10526–10531.

Brooks GA, Butterfield GE, Wolfe RR, Groves BM, Mazzeo RS, Sutton JR, Wolfel EE, Reeves JT (1991) Increased dependence on blood glucose after acclimatization to 4,300 m. J Appl Physiol 70: 919–927.

Buemi M, Cavallaro E, Floccari F, Sturiale A, Aloisi C, Trimarchi M, Grasso G, Corica F, Frisina N (2002) Erythropoietin and the brain: From neurodevelopment to neuroprotection. Clin Sci (Lond) 103: 275–282.

Buemi M Cavallaro E, Floccari F, Sturiale A, Aloisi C, Trimarchi M, Corica F, Frisina N (2003) The pleiotropic effects of erythropoietin in the central nervous system. J Neuropathol Exp Neurol 62: 228–236.

Cahan C, Decker MJ, Arnold JL, Washington LH, Veldhuis JD, Goldwasser E, Strohl KP (1992) Diurnal variations in serum erythropoietin levels in healthy subjects and sleep apnea patients. J Appl Physiol 72: 2112–2117.

Celik M, Gokmen N, Erbayraktar S, Akhisaroglu M, Konakc S, Ulukus C, Genc S, Genc K, Sagiroglu E, Cerami A, Brines M (2002) Erythropoietin prevents motor neuron apoptosis and neurologic disability in experimental spinal cord ischemic injury. Proc Natl Acad Sci U S A 99: 2258–2263.

Ceretelli P (1992) Muscle energetics and ultrastructure in chronic hypoxia. Respiration 59: 24–29.

Cheng Y, Gidday JM, Yan Q, Shah AR, Holtzman DM (1997) Marked age-dependent neuroprotection by brain-derived neurotrophic factor against neonatal hypoxic-ischemic brain injury. Ann Neurol 41: 521–529.

Chun YS, Hyun JY, Kwak YG, Kim IS, Kim CH, Choi E, Kim MS, Park JW (2003) Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. Biochem J 370: 149–157.

Clanton TL, Klawitter PF (2001) Adaptive responses of skeletal muscle to intermittent hypoxia: The known and unknown. J Appl Physiol 90: 2476–2487.

Digicaylioglu M, Lipton SA (2001) Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades. Nature 412: 641–647.

Dirnagl U, Simon RP, Hallenbeck JM (2003) Ischemic tolerance and endogenous neuroprotection. Trends Neurosci 26: 248–254.

D'Souza SP, Davis M, Baxter G (2004) Autocrine and paracrine actions of natriuretic peptides in the heart. Pharmacol Ther 101: 113–129.

Eid T, Brines M (2002) Recombinant human erythropoietin for neuroprotection: what is the evidence? Clin Breast Cancer (Suppl) 3: S109–115.

Fletcher EC (2000) Effect of episodic hypoxia on sympathetic activity and blood pressure. Respir Physiol 119: 189–197.

Franklin KA (2002) Cerebral haemodynamics in obstructive sleep apnoea and Cheyne-Stokes respiration. Sleep Med Rev 6: 429–441.

Galea E, Golanov EV, Feinstein DL, Kobylarz KA, Glickstein SB, Reis DJ (1998) Cerebellar stimulation reduces inducible nitric oxide synthase expression and protects brain from ischemia. Am J Physiol 274: H2035–2045.

Gleeson K, Zwillich CW, White DP (1990) The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis 142: 295–300.

Golanov EV, Zhou P (2003) Neurogenic neuroprotection. Cell Mol Neurobiol 23: 651–663.

Golanov EV, Liu F, Reis DJ (1998) Stimulation of cerebellum protects hippocampal neurons from global ischemia. Neuroreport 9: 819–824.

Gozal D, Lipton AJ, Jones KL (2002) Circulating vascular endothelial growth factor levels in patients with obstructive sleep apnea. Sleep 25: 59–65.

Grimm C, Wenzel A, Groszer M, Mayser H, Seeliger M, Samardzija M, Bauer C, Gassmann M, Reme CE (2002) HIF-1-induced erythropoietin in the hypoxic retina protects against light-induced retinal degeneration. Nat Med 8: 718–724.

Halliwill JR (2003) Hypoxic regulation of blood flow in humans. Skeletal muscle circulation and the role of epinephrine. Adv Exp Med Biol 543: 223–236.

Han BH, Holtzman DM (2000) BDNF protects the neonatal brain from hypoxic-ischemic injury in vivo via the ERK pathway. J Neurosci 20: 5775–5781.

Han BH, D'Costa A, Back SA, Parsadanian M, Patel S, Shah AR, Gidday JM, Srinivasan A, Deshmukh M, Holtzman DM (2000) BDNF blocks caspase-3 activation in neonatal hypoxia-ischemia. Neurobiol Dis 7: 38–53.

Hossmann KA (1999) The hypoxic brain. Insights from ischemia research. Adv Exp Med Biol 474: 155–169.

Hu X, Kang J, Xiao D, Wang W, Hou X, Yu R (2002) The influence of nasal continual positive airway pressure on some vasoactive substances in patients with obstructive sleep apnea syndrome (in Chinese). Zhonghua Jie He He Hu Xi Za Zhi 25: 36–38.

Javeshghani D, Sakkal D, Mori M, Hussain SN (2000) Regulation of diaphragmatic nitric oxide synthase expression during hypobaric hypoxia. Am J Physiol Lung Cell Mol Physiol 279: L520–527.

Jung F, Palmer LA, Zhou N, Johns RA (2000) Hypoxic regulation of inducible nitric oxide synthase via hypoxia inducible factor-1 in cardiac myocytes Circ Res 18: 319–325.

Jurkovicova I, Celec P, Mucska I, Hodosy J (2003) On the origin of cardiovascular complications of sleep apnea syndrome by the means of molecular interactions. Bratisl Lek Listy 104: 167–173.

Juul S (2002) Erythropoietin in the central nervous system, and its use to prevent hypoxic-ischemic brain damage. Acta Paediatr Suppl 91: 36–42.

Kalialis LV, Olsen NV (2003) Erythropoietin--a new therapy in cerebral ischemia? (in Danish). Ugeskr Laeger 165: 2477–2481.

Kiemer AK, Vollmar AM, Bilzer M, Gerwig T, Gerbes AL (2000) Atrial Natriuretic Peptide reduces expression of TNF-a mRNA during reperfusion of the rat liver upon decreased activation of NF-kappaB and AP-1. J Hepatol 33: 236–246.

Kirino T (2002) Ischemic tolerance. J Cereb Blood Flow Metab 22: 1283–1296.

Lanfranchi P, Somers VK (2001) Obstructive sleep apnea and vascular disease. Respir Res 2: 315–319.

Lavie L (2003) Obstructive sleep apnoea syndrome – an oxidative stress disorder. Sleep Med Rev 7: 35–51.

Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, Lavie P (2002) Plasma vascular endothelial growth factor in sleep apnea syndrome: Effects of nasal continuous positive air pressure treatment. Am J Respir Crit Care Med 165: 1624–1628.

Lebuffe G, Schumacker PT, Shao ZH, Anderson T, Iwase H, Vanden Hoek TL (2003) ROS and NO trigger early preconditioning: relationship to mitochondrial KATP channel. Am J Physiol Heart Circ Physiol 284: H299–308.

McNamara SG, Aarts MJ, Becker H, Cao K, Polo OJ, Sullivan CE (1995) Ventilatory responses to repetitive hypoxia in subjects with obstructive sleep apnea. Am J Respir Crit Care Med 151: A100.

Mitchell GS, Baker TL, Nanda SA, Fuller DD, Zabka AG, Hodgeman BA, Bavis RR, Mack KJ, Olson EB (2001) Intermittent hypoxia and respiratory plasticity. J Appl Physiol 90: 2466–2475.

Mohsenin V (2001) Sleep-related breathing disorders and risk of stroke. Stroke 32: 1271–1278.

Mu D, Jiag X, Sheldon RA, Fox CK, Hamrick SE, Vexler ZS, Ferriero DM (2003) Regulation of hypoxia-inducible factor 1alpha and induction of vascular endothelial growth factor in a rat neonatal stroke model. Neurobiol Dis 14: 524–534.

Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 74: 1124–1136.

Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK (1999) Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 99: 1183–1189.

Navegantes LC, Resano NM, Migliorini RH, Kettelhut IC (2000) Role of adrenoceptors and cAMP on the catecholamine-induced inhibition of proteolysis in rat skeletal muscle. Am J Physiol Endocrinol Metab 279: E663–668.

Olsen NV (2003) Central nervous system frontiers for the use of erythropoietin. Clin Infect Dis 37 (Suppl.): S323–330.

Parati G, Ongaro G, Bonsignore MR, Glavina F, Di Rienzo M, Mancia G (2002) Sleep apnoea and hypertension. Curr Opin Nephrol Hypertens 11: 201–214.

Reis DJ, Golanov EV, Galea E, Feinstein DL (1997) Central neurogenic neuroprotection: Central neural systems that protect the brain from hypoxia and ischemia. Ann N Y Acad Sci 835: 168–186.

Remsburg S, Launois SH, Weiss JW (1999) Patients with obstructive sleep apnea have an abnormal peripheral vascular response to hypoxia. J Appl Physiol 87: 1148–1153.

Rogers TK, Sheedy W, Waterhouse J, Howard P, Morice AH (1994) Haemodynamic effects of atrial natriuretic peptide in hypoxic chronic obstructive pulmonary disease. Thorax 49: 233–239.

Sanchez-Elsner T, Ramirez JR, Rodriguez-Sanz F, Varela E, Bernabeu C, Botella LM (2004) Cross-talk between hypoxia and TGF-beta orchestrates erythropoietin gene regulation through SP1 and smads. J Mol Biol 336: 9–24.

Sato T, Sasaki N, O'Rourke B, Marban E (2000) Adenosine primes the opening of mitochondrial ATP-sensitive potassium channels: a key step in ischemic preconditioning? Circulation 102: 800–805.

Schaller B, Graf R (2002) Cerebral ischemic preconditioning. An experimental phenomenon or a clinical important entity of stroke prevention? J Neurol 249: 1503–1511.

Scheepens A, Wassink G, Blanco CE (2003) The effect of a global birth asphyxia on the ontogeny of BDNF and NGF protein expression in the juvenile brain. Brain Res Dev Brain Res 140: 215–221.

Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lucke C, Mayer K, Olschewski H, Seeger W, Grimminger F (2000) Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: Response to CPAP therapy. Thorax 55: 1046–1051.

Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F (2002) Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. Am J Respir Crit Care Med 165: 67–70.

Sharp FR, Bergeron M, Bernaudin M (2001) Hypoxia-inducible factor in brain. Adv Exp Med Biol 502: 273–291.

Schäbitz WR, Sommer C, Zoder W, Kiessling M, Schwaninger M, Schwab S (2000) Intravenous brain-derived neurotrophic factor reduces infarct size and counterregulates Bax and Bcl-2 expression after temporary focal cerebral ischemia. Stroke 31: 2212–2217.

Sinor AD, Greenberg DA (2000) Erythropoietin protects cultured cortical neurons, but not astroglia, from hypoxia and AMPA toxicity. Neurosci Lett 90: 213–215.

Siren AL, Fratelli M, Brines M, Goemans C, Casagrande S, Lewczuk P, Keenan S, Gleiter C, Pasquali C, Capobianco A, Mennini T, Heumann R, Cerami A, Ehrenreich H, Ghezzi P (2001a) Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. Proc Natl Acad Sci U S A 98: 4044–4049.

Siren AL, Knerlich F, Poser W, Gleiter CH, Bruck W, Ehrenreich H (2001b) Erythropoietin and erythropoietin receptor in human ischemic/hypoxic brain. Acta Neuropathol (Berl) 101: 271–276.

Somers VK, Dyken ME, Clary MP, Abboud FM (1995) Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96: 1897–1904.

Teramoto S, Kume H, Matsuse T, Ishii T, Miyashita A, Akishita M, Toba K, Ouchi Y (2003a) Oxygen administration improves the serum level of nitric oxide metabolites in patients with obstructive sleep apnea syndrome. Sleep Med 4: 403–407.

Teramoto S, Kume H, Yamamoto H, Ishii T, Miyashita A, Matsuse T, Akishita M, Toba K, Ouchi Y (2003b) Effects of oxygen administration on the circulating vascular endothelial growth factor (VEGF) levels in patients with obstructive sleep apnea syndrome. Intern Med 42: 681–685.

Thomas DD, Liu X, Kantrow SP, Lancaster JR jr. (2001) The biological lifetime of nitric oxide: Implications for the perivascular dynamics of NO and O2. Proc Natl Acad Sci U S A 98: 355–360.

Tun Y, Hida W, Okabe S, Kikuchi Y, Kurossawa H, Tabata M, Shirato K (2000) Effects of nasal continuous positive pressure on awake ventilatory responses to hypoxia and hypercapnia in patients with obstructive sleep apnea. Tohoku J Exp Med 190: 157–168.

Vanden Hoek TL (2002) Preconditioning and postresuscitation injury. Crit Care Med 30 (Suppl.): S172–S175.

Vanden Hoek TL, Becker LB, Shao Z, Li C, Schumacker PT (1998) Reactive oxygen species released from mitochondria during brief hypoxia induce preconditioning in cardiomyocytes. J Biol Chem 273: 18092–18098.

Weih M, Prass K, Ruscher K, Trendelenburg G, Dirnagl U, Riepe MW, Meisel A (2001) Ischemia tolerance; model for research, hope for clinical practice? (in German). Nervenarzt 72: 255–260.

Whyte KF, Allen MB, Jeffrey AA, Gould GA, Douglas N (1989) Clinical features of the sleep apnea/hypopnea syndrome. Quart J Med 72: 659–666.

Wick A, Wick W, Waltenberger J, Weller M, Dichgans J, Schulz JB (2002) Neuroprotection by hypoxic preconditioning requires sequential activation of vascular endothelial growth factor receptor. Akt J Neurosci 22: 6401–6407.

Wiggins AK, Shen PJ, Gundlach AL (2003) Atrial natriuretic peptide expression is increased in rat cerebral cortex following spreading depression: Possible contribution to sd-induced neuroprotection. Neuroscience 118: 715–726.

Xu F, Severinghaus JW (1998) Rat brain VEGF expression in alveolar hypoxia: Possible role in high-altitude cerebral edema. J Appl Physiol 85: 53–57.

Yamakawa M, Liu LX, Date T, Belanger AJ, Vincent KA, Akita GY, Kuriyama T, Cheng SH, Gregory RJ, Jiang C (2003) Hypoxia-inducible factor-1 mediates activation of cultured vascular endothelial cells by inducing multiple angiogenic factors. Circ Res 93: 664–673.

Yellon DM, Baxter GF, Garcia-Dorado D, Heusch G, Sumeray MS (1998) Ischaemic preconditioning: present position and future directions. Cardiovasc Res 37: 21–33.

Young T, Peppard PE, Gottlieb DJ (2001) Epidemiology of obstructive sleep apnea. A population health perspective. Am J Respir Care Med 165: 1217–1239.

Zhou J, Schmid T, Brune B (2003) Tumor necrosis factor-alpha causes accumulation of a ubiquitinated form of hypoxia inducible factor-1alpha through a nuclear factor-kappaB-dependent pathway. Mol Biol Cell 14: 2216–225.

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