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Anatomical basis of hypoxic and hyperoxic injuries to the centres of cardiorespiratory regulation

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Summary

The aim of the present paper is to briefly review the changes occurring in the nucleus tractus solitarii and carotid body in response to hypoxic and hyperoxic injuries. Selective alterations of dendrites and Fos-immunoreactivity of neurons have been observed in the subnucleus gelatinosus of the nucleus tractus solitarii of adult subjects dying after hypoxic-ischaemic injury. The selective vulnerability of this portion of the nucleus tractus solitarii may be explained mainly with reference to the vascularization of medullary tegmentum. In the carotid body, chronic hypoxia and hyperoxia cause a series of morphological, cellular and biochemical changes which may play a major role during the first postnatal period and may have implications in the pathogenesis of Sudden Infant Death Syndrome. Intermittent hypoxia may cause hypersensitivity of the carotid body, possibly increasing the risk of unstable respiration. Conversely, hyperoxia exposure has been reported to cause hyposensitivity and reduction in volume of the carotid body, possibly leading to ineffective response.

Key words

Nucleus tractus solitarii; carotid body; hypoxia; hyperoxia.

Introduction

The centres of cardiorespiratory regulation are mainly located in the medulla oblongata and their actions are modulated by inputs arriving from peripheral structures, such as the carotid body, and directed to the nucleus tractus solitarii (NTS). Hypoxic and hyperoxic stimuli may affect these peripheral and central nervous structures producing morphologic and functional changes. The aim of the present paper is to briefly outline the anatomical basis of hypoxia- and hyperoxia-induced changes in the NTS and carotid body.

Hypoxic/ischaemic injuries to the Nucleus Tractus Solitarii

Quite specific anatomic patterns of necrosis have been reported in the medulla oblongata of neonates with perinatal hypoxia and adults with hypoxic-ischaemic injury (Gilles, 1969; De Caro et al. 2000, 2003; Parenti et al. 2005). Selective lesion of dendrites has been observed in the dorsal portion of the NTS of adults who died after an episode of acute heart failure with profound and prolonged hypotension. The limited extent of these lesions were explained as selective necrosis of neurons

with greater vulnerability and excitotoxicity was suggested to contribute to ischaemic cell death (De Caro et al., 2000; 2003). The presence of the above selective hypereosinophilic areas has also been confirmed in cases characterised by shorter intervals of time between injury and death. Analysis of the sections following the subdivision of the NTS according to McRitchie and Tork (1993) revealed the hypereosinophilic roundish areas to be in the subnucleus gelatinosus (Porzionato et al., 2004). The strong hypereosinophilic appearance and shrinking of neurons supported the vitality and the hypoxic-ischaemic origin of the lesion and the hypothesis of excitotoxic death. The early neuronal lesion in selective neuronal necrosis due to hyperexcitation does involve neuronal dendrites, which appear to swell because of loss of ion and water homeostasis, whereas other tissue elements, such as astrocytes, neuronal perikarya or axons, escape this process because of fewer glutamate receptors.

The vitality and the hypoxic-ischaemic origin of lesions was also supported by strong, selective Fos-like immunoreactivity. The expression of Fos has mainly been associated with cell damage and subsequent death following hypoxic-ischaemic injury and has been shown to be specifically involved in glutamate-mediated cell death.

The selective involvement of the subnucleus gelatinosus in the context of the NTS can be explained mainly by reference to the vascularization of the medullary tegmentum, since the NTS is located at the watershed zone between the terminal branches of the three areas of vascularization described by Foix and Hillemand (1925), i.e., a median area fed by the paramedian arteries to the motor nuclei, a middle area fed by the short circumferential arteries, and a lateral area fed by the posterior inferior cerebellar artery (Macchi et al., 2004).

Neurons may also undergo apoptosis in response to hypoxic-ischaemic injury (Rebuffat et al., 2002; Belloni et al., 2003) and the distribution of apoptosis of neurons and glial cells in the medullary nuclei of infant and adult subjects who died of hypoxic-ischaemic injury has been studied through the optical dissector method (Stecco et al., 2005; Porzionato et al., 2008a; 2009a) in order to identify possible anatomy- and age-related patterns. The neuronal apoptotic indexes of infants were lower than those of adults, with statistical significance for NTS and some other nuclei, indicating different characteristics of survival between adults and infants. Heterogeneity was found among the neuronal apoptotic indexes of the various nuclei of the medulla oblongata, indicating different vulnerability of the medullary nuclei in response to hypoxic-ischaemic injury.

Hypoxic and hyperoxic changes in the carotid body

The carotid body is composed of lobules of cells belonging to two separate populations: type I cells contain many dense-cored vesicles storing biogenic amines and neuropeptides, such as adrenomedullin and galanin (Belloni et al., 2001; Macchi et al., 2006; Porzionato et al., 2006; 2010; Rebuffat et al., 2007; Tortorella et al., 2007), and are generally considered to be the real chemoreceptors of the carotid body; type II cells mainly have a structural function. The carotid body does not contribute greatly to breathing during fetal life but, in the following postnatal period, a gradual increase in hypoxic chemosensitivity and in the slope of the hypoxic stimulus-response curve develops (Gauda et al., 2004; Porzionato et al., 2008b).

In the carotid body, chronic hypoxia and hyperoxia cause a series of morphological, cellular and biochemical changes which may play a major role during the first postnatal period. In chronic hypoxia due to lung or congenital heart diseases carotid bodies have been found to be enlarged, with a percent increase in type II cells. The percentage of type I cells has been reported to decrease in chronic obstructive pulmonary disease and to increase in chronic high-altitude hypoxia. Chronic hypoxia has been shown to increase O_2 sensitivity in the carotid body through changes in chemoreceptor molecules, ion channels and neurochemicals (Powell, 2007). NADPH oxidase plays an important role in plasticity during chronic hypoxia, producing a great amount of superoxide which may enhance the effects of other neuromodulators. Decreased K^+ channel density and increased Na^+ and Ca^{2+} channels density have been found in glomus cells cultured in conditions of chronic hypoxia and in carotid bodies of chronically hypoxic neonatal rats.

In human infants, many authors have found that exposure to tobacco smoke alters hypoxic arousal and ventilation responses (Gauda et al., 2004). Experimental studies on animals also confirmed such findings in prenatal tobacco smoke exposure. In newborn rats, reduction of hypoxic ventilation and autoresuscitation after repeated asphyxia were found. Hafstrom et al. (2002) reported reduced ventilation and arousal responses to hypoxia during sleep in newborn lambs. Peripheral chemoreceptors play a major role in the regulation of these physiological responses, so that all these findings support the hypothesis that prenatal nicotine alters the function of these chemoreceptors and may play a role in the pathogenesis of sudden infant death syndrome (SIDS; Gauda et al., 2004; Porzionato et al., 2008b, 2009b). The literature also contains experimental reports on animals which investigate the effect of postnatal exposure to hypoxia on the carotid body. Wang and Bisgard (2005) revealed increases in BrdU-positive and total type I cells after one week of hypoxia (12% O_2) and increases in tyrosine hydroxylase and sinaptophysin immunoreactivities.

Morphological and functional effects of postnatal hyperoxia on the carotid body have also been studied in rats. Wang and Bisgard (2005) found that 60% hyperoxia produced decreases in proliferating and total type I cells, with decrease in tyrosine hydroxylase and sinaptophysin contents. Erickson et al. (1998) found a decreased number of unmyelinated sensory nerve fibers and of tyrosine hydroxylase-positive stained neurons in the petrosal ganglion following exposure to hyperoxia for the first four postnatal weeks. Reduced volume of the adult carotid body has been reported in the literature after postnatal exposure to 60% hyperoxia (Bisgard et al., 2003). Di Giulio et al. (1998) reported focal necrosis, increase of endoplasmic reticulum, Golgi apparatus, and mitochondria volume in type I cells of carotid bodies of adult rats exposed to 98-100% hyperoxia for 60-65 hours.

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