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Morphological changes in the rat carotid body following acute sodium nitrite treatment

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ABSTRACT

The carotid body (CB) is a small neural crest-derived chemosensory organ that detects the chemical composition of the arterial blood and responds to its changes by regulating breathing. The effects of acute nitrite treatment on the CB morphology in rats were examined by morphometry. We found that 1 h after administrating a single dose of sodium nitrite, the CB underwent structural changes characterized by a prominent increase in its size with a marked, several-fold dilation of the blood vessels. The obvious CB enlargement mostly due to apparent vasodilation and glomus cell hypertrophy was at its highest one day later and persisted until the fifth day. 20 days after the treatment, the CB regained its size to the normoxic control state. Morphometric analysis revealed that the CB size increase in treated animals is statistically significant when compared to that of untreated controls. It can be inferred that the nitrite-exposed CB displays remarkable structural plasticity and enlarges its size mostly through vascular expansion.

1. Introduction

The carotid body (CB) is a polymodal peripheral chemoreceptor that registers the levels of pO2, pCO2 and pH in the arterial blood (Gonzalez et al., 1994; Prabhakar and Joyner, 2015). It plays an essential role in initiating an appropriate respiratory and cardiovascular response to hypoxia, hypercapnia and acidosis, leading to the restoration of blood gas homeostasis (reviewed in Gonzalez et al., 1994 and recently by Kumar and Prabhakar, 2012). The organ consists of cell clusters of two cell types, i.e. neuron-like glomus (or type I) cells and glial like sustentacular (or type II) cells, intermingled with a dense network of fenestrated capillaries and nerve bundles, and separated by connective tissue (Gonzalez et al., 1994; Verna, 1997; Atanasova et al., 2011; Kumar and Prabhakar, 2012).

It is well-known that chronic hypoxia induces gene expression, leading to profound morphological changes at a cellular level in the CB (Wang and Bisgard, 2002; Kusakabe et al., 2005). A number of previous studies have described the structural alterations in the rat CB upon exposure to sustained hypoxia (Laidler and Kay, 1975; McGregor et al., 1984; Lahiri et al., 2000; Kusakabe et al., 2005; Matsuda et al., 2006; Pardal et al., 2007). It has been revealed that in humans the long-term hypoxia caused a several-fold increase of the CB size mostly due to marked vasodilation and hyperplasia of the glomus cells (Heath et al., 1985), or their hypertrophy in rats (Wang and Bisgard, 2002; Wang et al., 2008). Such a morphological adaptive response to prolonged hypoxia occurs during acclimatization to high altitudes (Arias-Stella and Valcarcel, 1976; Wang and Bisgard, 2002). Conversely, no definite evidence concerning a volume increase of glomus cells in the rats exposed to short-term (for up to 24 h) hypoxia has been provided so far (see Kato et al., 2010 and references therein).

On the other hand, the mechanisms of the origin of hypoxia are exceptionally diverse and their exact effects on the CB morphology remain to be established. It has recently been proposed that one putative hypoxia-sensing mechanism is the production of oxygen radicals (López-Barneo et al., 2008). It is also established that the repeated episodes of hypoxia-reoxygenation produce local oxidative stress in the CB due to accumulation of reactive oxygen species (ROS), and their increased levels result in enhanced chemosensory response to hypoxia and cellular damage (Del Rio et al., 2010; Iturriaga and Del Rio, 2012). Nonetheless, since no chemosensory excitatory effects of ROS have been registered, the direct involvement of ROS in the transduction of oxygen levels in the CB has been questioned (Gonzalez et al., 2007). Furthermore, the morphological

Abbreviations: CB, carotid body; ET-1, endothelin-1; $NaNO_2$, sodium nitrite; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species.

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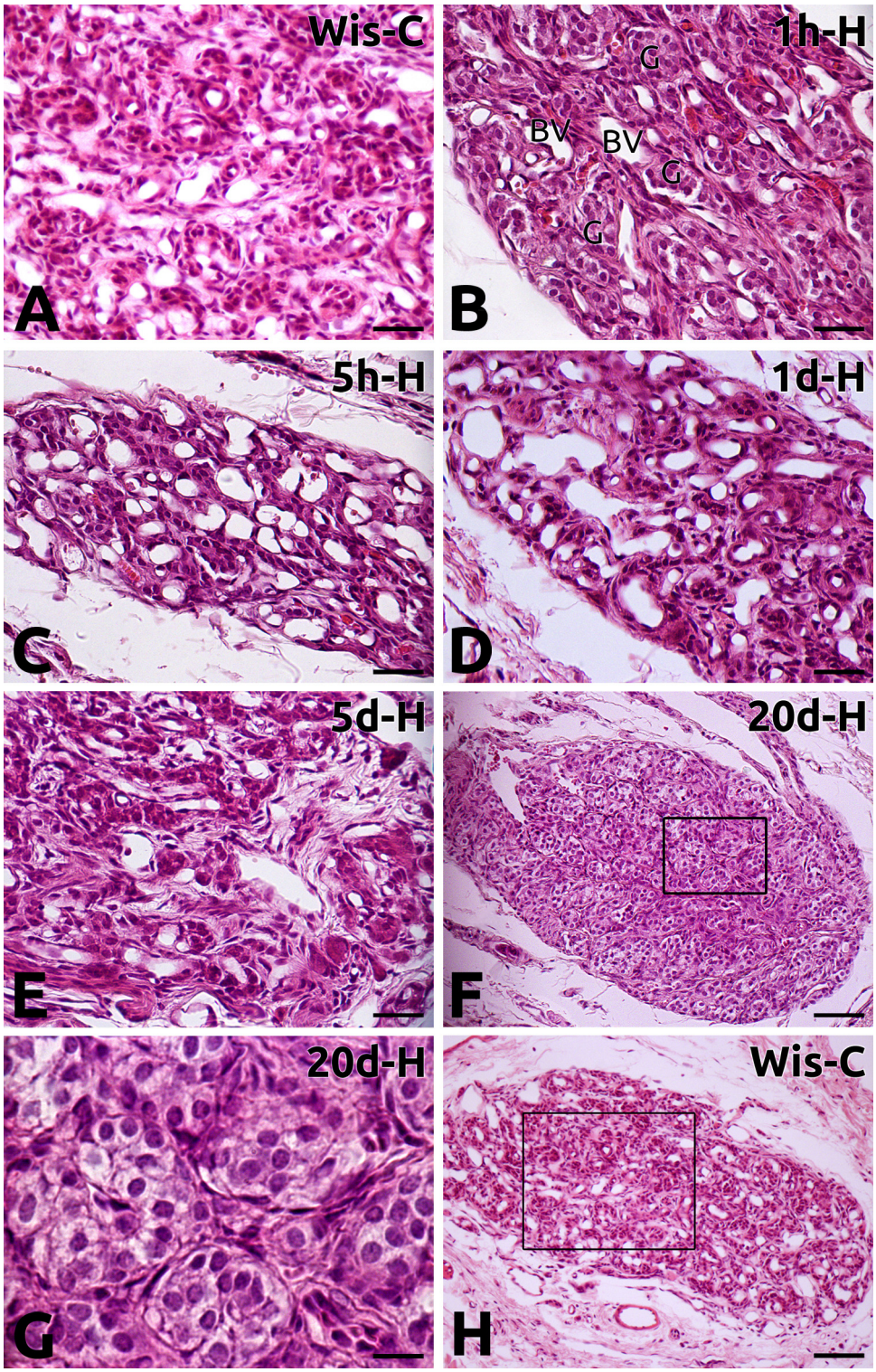

Fig. 1. Conventional hematoxylin and eosin (H&E) stained sections showing the morphological characteristics of the carotid body (CB) in normoxic and hypoxic rats. (A) A section from the control normoxic CB. High-power view of the area inside the rectangle in (H). (B) CB morphology 1 h after acute sodium nitrite-induced hypoxia. Note the slight enlargement of its size. The glomic clusters (G) are compact and surrounded by slightly distended blood vessels (BV). (C) 5 h following hypoxic exposure, a marked vasodilation in the CB is observed without apparent glomus cell hypertrophy. (D) Morphological changes of the CB 1 day later. Note the increased CB size and dilated blood vessels. (E) Representative photomicrograph showing the persistent vasodilation 5 days following hypoxic exposure. (F) H&E-stained sections from the hypoxic CB 20 days after hypoxic termination. Note that the hypoxic CB has almost the same size as its normoxic state (H) but the parenchyma is more compact. (G) High power view of the boxed area in the previous figure illustrating the morphological features of recovering CB. Note the compact glomeruli and hypertrophic glomus cells. The blood vessels have relatively narrower lumens and the extracellular matrix is somewhat expanded. Scale bar = 100 μm (F and H); 50 μm (B–E); 25 μm (G).