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Institutionen för Fysiologi och Farmakologi
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THE HUMAN CAROTID BODY

in sensing and signaling of oxygen and inflammation

AKADEMISK AVHANDLING

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ABSTRACT

Oxygen is essential for cell survival and global oxygenation is closely monitored in order to protect tissues from hypoxic damage. The carotid body is an important systemic oxygen sensor responding to hypoxia and a multitude of other blood borne stimuli, including inflammatory mediators. Activation of the carotid body by depolarization of the chemosensitive type 1 cells ultimately leads to appropriate ventilatory and cardiovascular responses. While animal carotid body oxygen sensing and signaling is extensively studied, this is essentially uncharacterized in the human carotid body. The aim of this thesis was to investigate the human carotid body in terms of morphology, global and specific expression of oxygen sensing and signaling genes as well as inflammatory response genes. To assess the response to hypoxia, slices of the human carotid body were exposed to acute or prolonged hypoxia and release of ACh, ATP and cytokines was measured. In order to evaluate the human carotid body gene expression profile it was compared to the carotid body gene expression from two mouse strains as well as functionally related tissue transcriptomes.

The human carotid body revealed a specific tissue gene expression profile with enrichment of genes related to angiogenesis and inflammation when compared to brain and adrenal gland and showed a neurological profile in comparison to adrenal gland. Specific expression of genes related to oxygen sensing was demonstrated such as K^+ channels, enzymes synthesizing gaseous messengers and proteins involved in ROS-turnover and energy status. Despite many important similarities to animals, differences exist, for instance in expression of oxygen sensitive K^+ channels. Our data suggest TASK-1, Maxi-K or both as potential oxygen sensitive K^+ channels in the human carotid body. The Maxi-K splice variant ZERO that is more sensitive to hypoxic regulation than the Strex splice variant is the exclusively expressed isoform in the human carotid body.

Furthermore, the human carotid body expresses nicotinic acetylcholine and $GABA_A$ receptor subunits known as important targets for anesthetic agents, as well as purinergic receptors and the dopamine D_2 receptor. With few exceptions this is similar to the receptor map that we demonstrated in mouse carotid bodies. When exposed to acute hypoxia the human carotid body increases the release of ACh and ATP. This confirms findings in animal models where ACh and ATP are considered excitatory neurotransmitters.

Finally, the human carotid body expresses cytokines in the early and late inflammatory response as well as corresponding receptors and shows an overexpression of this group of genes compared to functionally related tissues. During prolonged hypoxia the human carotid body moreover releases pro- and anti-inflammatory cytokines.

In conclusion, we have studied human carotid body morphology, gene expression and hypoxia-induced neurotransmitter and cytokine release. We found similarities but also differences in the expression of key genes in oxygen sensing and signaling compared to the animal carotid body. Furthermore, the human carotid body has a structural and functional capacity to play a role in sensing and mediating systemic inflammation.

Key words: carotid body, oxygen sensing, oxygen signaling, chemosensor, hypoxic ventilatory response, hypoxia, gene expression, inflammatory response, receptor, K^+ channels, acetylcholine, ATP, cytokine release.