CENTRAL MECHANISMS INVOLVED IN THE SYMPATHOEXCITATION IN RESPONSE TO HYPOXIA

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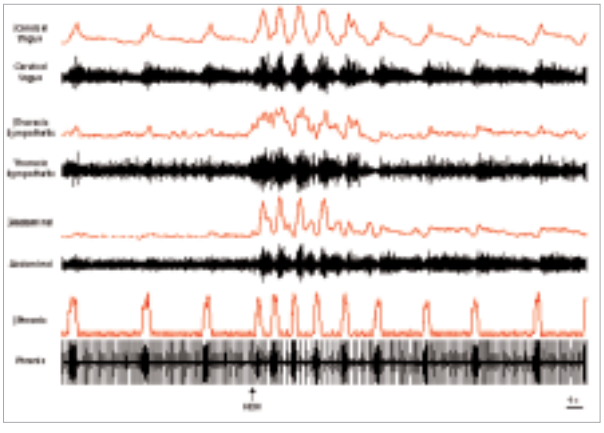


Raw and integrated (f) simultaneous recordings of the activity of cervical vagus, thoracic sympathetic, abdominal and phrenic nerves in the working-heart brainstem preparation during the activation of peripheral chemoreflex with potassium cyanide (arrow) in a rat previously submitted to chronic intermittent hypoxia

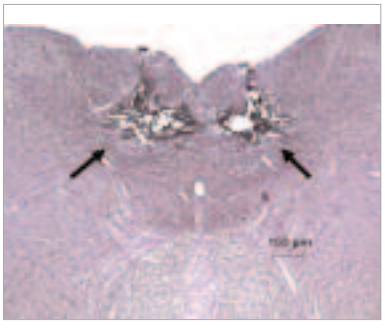
Hypoxia is a possible physiological and pathophysiological situation that plays a major role in the activation of the peripheral chemoreceptors, which produce the correspondent autonomic, respiratory and behavioral responses in order to provide the system with the appropriated level of oxygen in the arterial blood. The acute chemoreflex activation produces the necessary increased activity in the sympathetic nerve to provide the cardiovascular system with the level of vascular resistance required to increase the arterial blood flow to the upper part of the body and preserve the central nervous system from any hypoxic situation. However, the chronic activation of the peripheral chemoreceptors in physiopathological circumstances, such as the chronic intermittent hypoxia, may result in a persistent increase in the level of the sympathetic outflow, which, in turn, may result in arterial hypertension, i.e., another physiopathological situation.

The main focus of this project is the study of several aspects of the neurotransmission of the chemoreflex in different areas of the brain involved in the generation and modulation of the sympathetic nerve activity. Among several neurotransmitter systems, we will evaluated the possible role of the glutamatergic and purinergic systems in the processing of the sympathoexcitatory component of the chemoreflex in the nucleus tractus solitary (NTS), rostral ventrolateral medulla (RVLM) and the paraventricular nucleus of the hypothalamus (PVN), due to a series of previous experimental evidences about the possible involvement of these systems.

The work to be conducted is based upon our previous experience with the pharmacological studies of the brainstem areas in awake and anesthetized rats as well as our more recent experience with electrophysiology and immunocytochemistry. Two major experimental models are envisaged: the acute (KCN) and the chronic activation of the peripheral chemoreceptors. The experiments to be performed as well as the different experimental protocols to be used are divided in 13 sub-projects: functional and pharmacological (7), electrophysiological (4) and immunohistochemical approaches (2).

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The double antagonism of L-glutamate and ATP receptors in the NTS of awake rats produced a large increase in the baseline MAP and we used sodium nitroprusside infusion to normalize MAP. Under this experimental condition, chemoreflex was activated, and we verified that the double antagonism of L-glutamate and ATP receptors almost abolished the pressor response to chemoreflex activation, an antagonism that was reversible. Considering that the record of the sympathetic nerve activity in awake rats, combined with microinjections into the NTS, is not a simple task, we decided to use the working heart-brainstem preparations (WHBP) to verify the effect of bilateral microinjections of PPADS into the commissural NTS on the autonomic and respiratory responses to chemoreflex activation. The data obtained showed that the chemoreflex responses were not affected by bilateral microinjection of PPADS, an antagonism of P2X receptors. On the next experimental protocols in the WHBP, we used the double antagonism with kynurenic acid and PPADS. This combination, similarly to the findings in awake rats, was effective in blocking the sympathoexcitatory response to chemoreflex activation. Therefore, the data obtained in the WHBP not only confirmed he previous observation in awake rats, but also extended it to the concept that the effective antagonism of the sympathoexcitatory component of the chemoreflex was possible only when we combined the antagonism of L-glutamate and ATP receptors in the caudal commissural NTS. The findings that only the double antagonism was effective in blocking the sympathoexcitatory component of the chemoreflex open several interesting perspectives for further studies to better evaluate the central mechanisms involved in hypertension induction.



Example of a coronal section of the brainstem showing the microinjection sites (arrowheads) at the caudal portion of the rat solitary tract nucleus

MAIN PUBLICATIONS

Silva de Oliveira LC, Bonagamba LG, Machado BH. 2007. Noradrenergic inhibitory modulation in the caudal commissural NTS of the pressor response to chemoreflex activation in awake rats. *Auton Neurosci*. **136(1-2)**:63-8.

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