The arterial chemoreflex increases ventilation, sympathetic nervous system activity, and arterial blood pressure to maintain oxygen delivery in hypoxic conditions. Chemosensors in the aortic and carotid bodies sense arterial oxygen, and chemoreceptors convey this information to the nucleus tractus solitarii (NTS) in the brainstem. The NTS integrates this input and sends signals to nuclei in the brainstem and spinal cord involved in chemoreflex control. The output from the NTS to the ventrolateral medulla (VLM) is considered to be the primary reflex pathway mediating autonomic and ventilatory responses to hypoxia. Another pathway contributing to the response to hypoxia is a projection from the NTS to the hypothalamo-pituitary axis (PVN). The PVN is an integral component in control of respiration, cardiovascular function, and sympathetic nerve activity. Hypoxia activates (indicated by Fos immunoreactivity, IR) NTS projections to the PVN, and the response to hypoxia is blunted when the PVN is inhibited or lesioned. Together, these data suggest the PVN is important in control of sympathetic, pressor, and respiratory responses to hypoxia. However, the afferent pathway from the PVN that mediates cardiovascular responses to hypoxia is not fully understood. The PVN sends projections to the VLM and spinal cord nuclei involved in control of respiration and sympathetic nervous system function; these projections, however, do not express Fos following hypoxia, indicating that they are not activated by the chemoreflex. Projections from the brainstem to the PVN to the NTS do express Fos after exposure to hypoxia, suggesting this pathway may contribute to chemoreflex responses. The majority of nTS-projecting PVN neurons express either oxytocin or CRH, in hypoxia, most (85-95%) activated nTS-projecting PVN neurons express CRH. Thus, the PVN may mediate responses to hypoxia via CRH acting on receptors in the NTS. We have shown that the predominant CRH receptor in the nTS, CRFR2, colocalizes extensively with oxytocin, and also with synaptophysin, suggesting CRH modulates oxytocin release in the nTS pre-synaptically.

Methods

Animals: Male Sprague Dawley rats (250-350g) were used; n=15 hypoxic (10% O2), n=15 normoxic (21% O2). Retrograde labeling from the VLM: Anterograde anterograde tracer Cholera toxin B (CtB): 1:3000, sc; Alexafluor 405 or 555) was injected bilaterally (30 nl, 400 nl). Following recovery from microinjection surgery, conscious rats were exposed to hypoxia for 10 min. NTS projections to the VLM were observed using photomicrographs of coronal sections of the hindbrain. Photomicrographs of coronal section of the VLM were analyzed for Fos and CtB expression. Neurons were counted in representative sections from each animal. The percentage of Fos and CtB-positive cells that colocalized was determined. Statistical analysis was performed using a two-tailed Student’s t-test. * p<0.05

Results

The majority of nTS-projecting PVN neurons express either oxytocin or CRH. In hypoxia, most (85-95%) activated nTS-projecting PVN neurons express CRH. Thus, the PVN may mediate responses to hypoxia via CRH acting on receptors in the NTS. We have shown that the predominant CRH receptor in the nTS, CRFR2, colocalizes extensively with oxytocin, and also with synaptophysin, suggesting CRH modulates oxytocin release in the nTS pre-synaptically.

Hypothetical model

• CRFR2 and oxytocin-expressing parvocellular neurons exhibit appositions onto oxytocin neurons that are activated in hypoxia, in particular VLM-projecting neurons.

Discussion

Our findings suggest that the VLM projecting CRH neurons interact with oxytocin neurons. These interactions may influence activation of VLM CRH neurons in chemoreflex responses. Further studies on the interactions between oxytocin and VLM-projecting nTS neurons are needed to elucidate the role of oxytocin in the chemoreflex responses.

Conclusion

Pretreatment of rats with oxytocin reduced the activation of VLM CRH neurons in hypoxic conditions. These findings support the hypothesis that oxytocin interacts with VLM-projecting CRH neurons and may influence chemoreflex responses. Further studies are needed to investigate the mechanisms underlying these interactions.

Future Directions

• Studies to evaluate the effects of oxytocin on VLM-projecting CRH neurons in chemoreflex responses
• Studies to evaluate the effects of oxytocin on VLM-projecting CRH neurons in chemoreflex responses

References

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