Abstract zur Dissertation von:
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Thema: Effects of neural nitric oxide gene inactivation on the neuroendocrine stress response in mice

Abstract

This study was undertaken to elucidate the role nitric oxide (NO) plays in the regulation of the stress response in mammals. As previous reports investigating this issue with the aid of pharmacological agents yielded conflicting results, we decided to use neural nitric oxide synthase (nNOS) KO mice as animal model to examine the activity of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-neurohypophyseal-system (HNS) and the sympatho-adrenal system (SAS) under physiological conditions and in response to a 10 minute-forced swimming session. Our findings suggest that, under basal conditions, NO inhibits vasopressin (AVP) gene transcription at the level of the supraoptic (SON), whereas it promotes it at the level of the paraventricular (PVN). Seemingly, its action is exercised through two mechanisms that differentially affect the activity of vasopressinergic neurones of the SON and the PVN, which supports the hypothesis of the existence of a functional diversity between the two hypothalamic nuclei. The reason of such a dichotomy might lie in the higher cellular complexity that characterises the PVN, which assembles different neuronal and glial cell types, and coordinates autonomic and neuroendocrine inputs in concert with other stressor-exposure sensitive brain areas, including the amygdala. A similar dichotomy appears evident also between vasopressinergic and oxytocinergic neurones, as mutant mice showed normal oxytocin (OXT) mRNA levels in both the SON and the PVN. Thus, NO of nNOS origin seems to modulate, at hypothalamic level, preferentially AVP production. The peripheral release of both neuropeptides under resting conditions in KO mice is unchanged, indicating that AVP and OXT secretion into the bloodstream from the neurohypophysis occurs as normal. Similarly, corticotropin-releasing hormone (CRH) mRNA at the hypothalamus as well as plasma adrenocorticotropic hormone (ACTH) and corticosterone (Cort) basal values were found to be unaffected by the absence of nNOS. Conversely, nNOS gene inactivation appeared to affect catecholamine biosynthetic enzymes, which are significantly reduced in KO mice, although this did not impair plasma norepinephrine (NE) and epinephrine (E) basal values. Overall, mutant mice manifest under resting conditions a mild phenotype, which is in accordance with previous observations.
However, upon acute stressor exposure NO seems to collaborate in maintaining constant AVP, OXT and E plasma profile release, as KO animals revealed anomalous AVP, OXT and E blood levels in response to forced swimming. The HPA-axis peripheral activity appeared to be affected only with respect to plasma Cort levels, which rose faster in KO than in WT mice following forced swimming. This is, however, not surprising, given the fact that we applied conditions of acute stressor exposure, and a direct effect of the absence of NO/nNOS on the HPA-axis is probably evident only under conditions of chronic stressor exposure. Further studies are necessary to investigate in mutant mice the response of this system to chronic stressor exposure.
Taken together, our findings suggest that NO may be an important intermediary in the network engaged in modulating the endocrine stress response, and might, therefore, be implicated in the pathophysiology of diseases, such as anxiety and depression, that reflect a dysregulation of the stress response.