Brain nitric oxide synthases in the interleukin-1β-induced activation of hypothalamic-pituitary-adrenal axis

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Abstract:
Background: Interleukin-1β (IL-1β), the major cytokine involved in activation of hypothalamic-pituitary-adrenal (HPA) axis modulates both central and peripheral components regulating HPA activity. The role of nitric oxide (NO) generated by neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) in brain structures involved in HPA axis regulation has not been elucidated. The aim of the study was to assess the receptor selectivity of IL-1β stimulatory action on HPA axis and to determine the involvement of nNOS and iNOS in this stimulation.

Methods: Experiments were performed on male Wistar rats which were injected intraperitoneally (ip) with IL-1β (5 μg/kg) or IL-1 receptor antagonist (IL-1ra) (50 μg/kg or 100 μg/kg) 15 min before IL-1β. Rats were sacrificed by rapid decapitation 1, 2 or 3 h after IL-1β administration. Trunk blood for ACTH, corticosterone and IL-1β determinations was collected and prefrontal cortex, hippocampus and hypothalamus were excised and snap frozen. Western blot analyses were performed and IL-1β, nNOS and iNOS protein were determined in brain structures samples.

Results: IL-1β significantly increased plasma ACTH, corticosterone and IL-1β levels during 2 h after ip administration. IL-1 receptor antagonist was able to abolish the stimulatory effect of IL-1β on plasma ACTH and corticosterone levels and significantly, but not totally, reduced plasma IL-1β level. The role of NO in prefrontal cortex, hippocampus and hypothalamus in the IL-1β-induced HPA axis activity alteration was determined by measuring the changes in nNOS and iNOS levels. The highest level of both isoforms 1 h following IL-1β administration decreased in a regular, parallel manner 2 and 3 h later, approaching control values. These changes were almost totally prevented by pretreatment with IL-1 receptor antagonist. In the hypothalamus the IL-1β-induced initial significant increase of nNOS regularly decreased in a modest rate and remained at significant higher level compared to control values. By contrast, iNOS level gradually increased 2 and 3 h after IL-1β administration in a significant time-dependent manner. The changes in both NO isoforms in both regions in hypothalamus were suppressed by pretreatment with IL-1 receptor antagonist. Results also show that a regular and parallel decrease of nNOS in the hypothalamus and prefrontal cortex are parallel in time and magnitude to respective fall in plasma IL-1β and ACTH levels.

Conclusion: The present study suggests that the IL-1β-induced transient stimulation of HPA axis activity is parallel in time and magnitude to the respective changes of nNOS in hypothalamus and prefrontal cortex, the brain structures involved in regulation of HPA axis activity.

Key words: interleukin-1 β, nitric oxide synthases, interleukin-1 receptor antagonist, immuno-endocrine responses, limbic-hypothalamic-adrenal axis