Role of Interleukin-1 in Stress Responses

A Putative Neurotransmitter

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Abstract

Recently, the central roles of interleukin-1 (IL-1) in physical stress responses have been attracting attention. Stress responses have been characterized as central neurohormonal changes, as well as behavioral and physiological changes. Administration of IL-1 has been shown to induce effects comparable to stress-induced changes. IL-1 acts on the brain, especially the hypothalamus, to enhance release of monoamines, such as norepinephrine, dopamine, and serotonin, as well as secretion of corticotropin-releasing hormone (CRH). IL-1-induced activation of the hypothalamo-pituitary-adrenal (HPA) axis in vivo depends on secretion of CRH, an intact pituitary, and the ventral noradrenergic bundle that innervates the CRH-containing neurons in the paraventricular nucleus of the hypothalamus. Recent studies have shown that IL-1 is present within neurons in the brain, suggesting that IL-1 functions in neuronal transmission. We showed that IL-1 in the brain is involved in the stress response, and that stress-induced activation of monoamine release and the HPA axis were inhibited by IL-1 receptor antagonist (IL-1Ra) administration directly into the rat hypothalamus. IL-1Ra has been known to exert a blocking effect on IL-1 by competitively inhibiting the binding of IL-1 to IL-1 receptors. In the latter part of this review, we will attempt to describe the relationship between central nervous system diseases, including psychological disorders, and the functions of IL-1 as a putative neurotransmitter.

Index Entries: Interleukin-1; stress responses; hypothalamo-pituitary-adrenal axis; interleukin-1 receptor antagonist; monoamine; corticotropin-releasing hormone; adrenocorticotropic hormone.

Central Stress Responses

Activation of the HPA Axis

Animals exposed to stressful stimuli exhibit responses causing adrenocorticotropic hormone (ACTH) secretion (Bilezikjian and Vale, 1983; Vale et al., 1983). ACTH is secreted in response to multiple stimuli by hypothalamic neuropeptides and neuronal monoamines, such as corticotropin-releasing hormone (CRH), vasopressin (VP), norepinephrine (NE), serotonin (5-HT), and so on. CRH is a major media-

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tor of ACTH release. ACTH enhances the secretion of glucocorticoids from the adrenal cortex (Bilezikjian and Vale, 1983; Vale et al., 1983). Glucocorticoids mediate many of the metabolic and immune aspects of the stress response, such as stimulation of hepatic gluconeogenesis, increase of metabolic rate, suppression of inflammation, and inhibition of immune reactions. Glucocorticoids also regulate the secretion of CRH and ACTH by an inhibitory feedback mechanism mediating type II glucocorticoid receptors, which are present at high concentrations in the hypothalamus, particularly in the CRH neurons (McEwen et al., 1968; Johnston et al., 1985).

In the case of animals exposed to sustained stress, the ACTH response manifests as a rapid increase followed by a decline toward normal levels despite the continuous presence of the stress (Keller-wood and Dallman, 1984; Hauger et al., 1988). It was suspected that a glucocorticoid feedback mechanism contributed to adaptation of the pituitary ACTH response in prolonged stress. However, the absence of glucocorticoids in adrenalectomized animals does not prevent the decline in ACTH secretion that normally occurs over a period of sustained stress (De Souza and Van Loon, 1982). Keller-wood and Dallman (1984) proposed that glucocorticoid feedback does not reduce ACTH responses during chronic stress. Such attenuation of the pituitary response in sustained stress may involve a number of mechanisms, including decreased hypothalamic secretion of CRH, exhaustion of the ACTH secretory capacity, and a decrease in pituitary receptors for ACTH regulators (Hauger et al., 1988). Hauger et al. (1988) reported that CRH receptor downregulation in the pituitary gland, after prolonged stress, results in partial desensitization of ACTH responses to CRH.

Further consideration of the finding that the absence of glucocorticoids in adrenalectomized animals does not prevent a decline in ACTH secretion during sustained stress (De Souza and Van Loon, 1982) is necessary, since this observation indicates that the glucocorticoid feedback mechanism is not the only system regulating this phenomenon. Whereas interaction between neural stimulatory effects on CRH and ACTH secretion and the inhibitory effects of glucocorticoids on these secretory activities have been investigated in considerable detail, questions persist as to what factors other than glucocorticoids are associated with decline of plasma ACTH levels toward normal levels, following a rapid increase, despite unabated stress. Gamma-aminobutyric acid (GABA) and opioid peptide have been suggested to participate in the inhibition of stress-induced CRH release, since these substances are known to be capable of inhibiting CRH release (Calogero et al., 1988).

On the other hand, in contrast with the participation of putative mechanisms for adaptation of the pituitary ACTH response to prolonged stress, ACTH responses to CRH or to novel stressful stimuli during prolonged stress were potentiated (De Souza and Van Loon, 1982). Although glucocorticoids downregulate their own receptors in many biological systems (Keller-wood and Dallman, 1984), this phenomenon occurs in a site-specific manner in the brain, namely in the hippocampus, septum, and amygdala but not in the hypothalamus or pituitary gland (Sapolsky et al., 1984). Hypothalamic-lesioned animals, in whom pituitary responsiveness to CRH is diminished by a glucocorticoid feedback signal, have been used to demonstrate that glucocorticoid-feedback inhibition can occur at the pituitary level (Jones et al., 1977). These findings suggest that the involvement of the negative feedback system is at the level of the hypophysis and the hypothalamus. The anatomical loci of such feedback inhibition and mechanisms to maintain the release of these hormones by overcoming the glucocorticoid negative feedback have been areas of major research interest.

Glucocorticoid Resistance Mechanism in the Hypothalamus

It has been suggested that VP may play a role in regulating pituitary responsiveness during chronic stress. VP was found not only to