HYPOTHALAMIC–PITUITARY-MEDIATED IMMUNOMODULATION: ARGININE VASOPRESSIN IS A NEUROENDOCRINE IMMUNE MEDIATOR

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SUMMARY
Organisms respond to a variety of environmental agents, such as those that cause inflammation, by mounting a coordinated complex series of adaptive responses involving the immune, nervous and endocrine systems. These adaptations are aimed at restoring the homeostatic balance and the return to the status quo ante. This interaction is facilitated by cytokines, hormones and neurotransmitters, as well as receptors that are endogenous to the neural, immune and endocrine systems. These shared ligands and receptors provide the molecular basis of this cross-talk. Studies of animal models of autoimmune diseases have shown that defects in the neuroendocrine immune communications contribute to the development of chronic inflammatory autoimmune disease. By analogy, similar observations have now been made in patients with inflammatory rheumatic disorders. For instance, patients with rheumatoid arthritis have abnormally low cortisol responses to inflammation, whilst the production of prolactin is excessive and dysregulated. Prolactin is a pro-inflammatory neuropeptide. This paper reviews the evidence to support the viewpoint that the neuropeptide arginine vasopressin, which is also produced by the hypothalamus, should be considered to be another neuroendocrine modulator of immune and inflammatory responses. It is also being hypothesized that the production of arginine vasopressin might be dysregulated and excessive in rheumatoid arthritis, and that this could be another additional neuroendocrine factor contributing to the pathophysiology of the disease.

KEY WORDS: Arginine vasopressin, Hypothalamus, Pituitary, Adrenal glands, Immune function, Inflammation.
Fig. 1.—The hypothalamus increases the release of AVP and CRH in response to inflammatory cytokines released from sites of inflammation. AVP and CRH synergize to increase ACTH production, which in turn stimulates the adrenal glands to secrete cortisol. Cortisol dampens inflammatory cytokines. The pituitary increases prolactin secretion in response to inflammatory stress. Prolactin and AVP potentiate local inflammation. CRH, corticotrophin release hormone; AVP, arginine vasopressin; Parvi, parvicellular neurone; SON, supraoptic neurones; +ve, stimulatory; −ve, inhibitory.

immune inflammatory disorders [23, 24]. Female Lewis (LEW/N) rats develop streptococcal cell wall peptidoglycan (SCW)-induced chronic arthritis [25] and experimental allergic encephalomyelitis [26], whilst the obese strain of chicken develops spontaneous autoimmune thyroiditis [26]. The susceptibility to developing chronic inflammatory diseases in Lewis rats, and to developing autoimmune thyroiditis in the obese strain of chicken, is directly linked to an inability to mount an adequate ACTH and corticosteroid response at the onset of inflammation [27–29]. This defect in Lewis rats is also be seen following injections of inflammatory cytokines such as IL-1β, and hypothalamic stimulants such as serotonin and quipazine. The histocompatible Fisher rats (F344/N) only develop acute transient polyarthritis, and mount a normal ACTH and corticosterone response [25, 28].

What is the relevance of these observations to human chronic autoimmune inflammatory disease? In humans, increased mortality to septicaemia is linked to defective cortisol responses to Gram-negative infections [30]. Patients with rheumatoid arthritis (RA) have defective hypothalamo–pituitary–adrenal axis responses to inflammation characterized by inappropriately low levels of circulating cortisol for the degree of joint inflammation [23, 24, 31–33] and excessive prolactin production [24, 34]. The latter observation is also found in patients with systemic lupus erythematosus (SLE), Reiter’s and primary Sjögren’s syndromes [35–37]. Prolactin is an important pro-inflammatory neuropeptide [11].

AVP production, like that of corticosteroids and prolactin, has a diurnal rhythm of secretion with a peak in the morning [38]. It is also involved in the exercise-induced stress response [39]. This paper reviews the evidence to support the viewpoint that AVP should be considered to be another pro-inflammatory hormone which exerts direct effects on immune and inflammatory responses. It is also proposed that its production is dysregulated in patients with RA and that this could be another additional contributory neuroendocrine factor in the pathophysiology of the disease.

THE REGULATION OF ARGinine VASOPRESSIN SECRETION

AVP is a nonapeptide produced by the magnocellular and parvicellular neurones of the paraventricular nucleus (PVN) of the hypothalamus, as well as the magnocellular neurones of the supraoptic nucleus (SON) [40–42]. The parvicellular neurones secrete both AVP and CRH into the median eminence where both pep-
tides are transported via the hypothalamic portal vessels to the pituitary [9]. SON cells have glucocorticoid receptors, whilst the PVN magnocellular AVP neurones appear not to, suggesting a direct modulation only of SON AVP neurones by corticosteroids [43, 44]. Magnocellular AVP reaches the hypothalamic portal system via the fenestrated capillaries of the subependymal plexus and the anterior pituitary via the vascular connections between the two lobes [45].

The release of AVP from the posterior pituitary is controlled by osmoreceptor cells situated in the anterior hypothalamus and the organonsum vasculosum of the lamina terminalis [10]. Other stimuli include hypotension, acute stress, morphine, nicotine, carbachol, chlorpromazine, hypoglycaemia and angiotensin II, whilst alcohol inhibits secretion [10]. Endothelins and atrial natriuretic peptide increase and decrease AVP secretion, respectively, in rats, but this remains to be determined in man [46, 47].

The gene for AVP in man is on chromosome 20p13, whilst in mice it is on chromosome 2 which also carries the IL-1 gene [48, 49]. The significance of the latter (if any) is unknown. In vitro, AVP gene expression and synthesis of hypothalamic AVP and CRH are positively regulated by catecholamines, acetylcholine, serotonin [73]. This observation is indicative of a role of AVP in immune function? The evidence reviewed above shows that AVP exerts pro-inflammatory and anti-inflammatory effects, whilst in mice it is on chromosome 2 which also carries the IL-1 gene [48, 49]. The significance of the latter (if any) is unknown. In vitro, AVP gene expression and synthesis of hypothalamic AVP and CRH are positively regulated by catecholamines, acetylcholine, serotonin [73]. This observation is indicative of a role of AVP in immune function?

THE FUNCTIONS OF ARGinine VASOPRESSIN

The physiological effects of AVP are, first, the antidiuretic effects [10] and, second, synergizing with CRH in stimulating ACTH production [9]; thus, it participates in modulating inflammatory responses. It is also a vasoconstrictor peptide [10] and can alter behaviour and learning, as well as cognitive functions [52, 53]. These effects are mediated via V1a, V2 and V3 receptors that show a differential tissue distribution [54–57]. This raises the possibility of selective inhibition. V3 receptors mediate the vascular effects [54] and are subdivided into V3a receptors found on hepatocytes and V3b in the pituitary [56]. V2 receptors mediate renal effects, whilst the putative V1b receptors are thought to mediate the behaviour and learning functions [57].

THE EFFECTS OF ARGinine VASOPRESSIN ON IMMUNE FUNCTION

What is the evidence for the relevance of AVP to immune function? In vitro, AVP augments autologous mixed lymphocyte responses [58]. This effect is dose dependent and can be blocked by V1 receptor inhibitors [58, 60]. AVP can replace the IL-2 requirement for interferon gamma (IFN-γ) production [59, 60]. High-affinity V1 receptors are found on human peripheral blood mononuclear cells and splenic lymphocytes [61, 62]. Thus, the existence of these receptors on inflammatory cells suggests that AVP has potential immunomodulatory properties. In experimental animals, AVP potentiates primary antibody responses in vivo [53]. As reviewed above, Lewis (LEW/N) rats are highly susceptible to developing severe chronic inflammatory diseases, whereas the histocompatible Fischer rats (F344/N) are resistant [25]. The Lewis rats also have a significantly high plasma concentration, hypothalamic content and in vitro release of AVP (and not oxytocin) in comparison with the F344/N rats [63, 64]. It is possible that these findings might represent a compensatory adaptation to deficient CRH and corticosterone secretion. Since systemic immunoneutralization of AVP in Lewis rats attenuates inflammatory responses, the high levels of circulating AVP are therefore an additional neuroendocrine factor contributing to the susceptibility to developing chronic inflammatory disease [65, 66]. The low levels of corticosterone and high levels of circulating AVP would favour the development of a predominantly Th1 cellular response and the generation of arthritogenic T cells [67].

The effects of IL-1β, TNF-α and IL-6 on the magnocellular AVP system are not fully characterized [4, 68, 69]. However, most studies in rats suggest a stimulatory effect of IL-1β on AVP secretion [70–72]. IL-1β and TNF-α are potent inducers of fever [10]. AVP attenuates endotoxin-induced fever via V1 receptors in rats [73]. This observation is indicative of a role of AVP in the neuroendocrine responses to inflammation.

In addition to augmenting the release of ACTH by the pituitary, AVP can potentiate the secretion of prolactin in Sprague–Dawley rats [74]. Whether enhanced AVP secretion is the mechanism responsible for the excessive and dysregulated secretion of prolactin seen in patients with SLE, RA, Sjögren’s and Reiter’s syndromes remains to be determined. Such a link could be of relevance to disease pathophysiology since both hormones are pro-inflammatory. On the other hand, infusions of substance P increase serum levels of AVP in a dose-dependent manner whilst inhibiting ACTH release [75, 76]. Since there is evidence that AVP is pro-inflammatory, excessive production of AVP in man may contribute to the susceptibility to developing chronic inflammation.

IMPLICATIONS FOR HUMAN DISEASE

The evidence reviewed above shows that AVP exerts pro-inflammatory effects on immune cells. Patients with RA have defective hypothalamic–pituitary–adrenal axis responses to inflammation with low levels of corticosteroids for the degree of joint inflammation, a situation reminiscent of the Lewis rat [8, 23, 25, 28, 31–33]. Thus, RA patients, like the Lewis rat, have a pro-inflammatory hormonal milieu which may contribute to the chronicity of the disease. In Lewis rats, the lack of a corticosterone response to inflammation associated with deficient ACTH production, but with increased production of CRH in inflamed joints and high levels of plasma AVP, contributes to the susceptibility to the development of inflammatory disease [25, 28, 63, 66]. A pro-inflammatory role for AVP in the neuroendocrine immunopathophysiology of inflammatory disease in Lewis rats is supported by the fact that systemic immunoneutralization of AVP attenuates
inflammatory responses [65]. Invoking direct human implications might be premature at the moment. CRH is pro-inflammatory and is produced in the joints of RA patients, where it might potentiate inflammation [77]. It can be hypothesized that its functional companion AVP might be secreted into joints in a similar manner or, if present in excessive levels in the circulation, could enhance chronic inflammation. Excessive prolactin production plays a role in the pathophysiology of experimental SLE, autoimmune uveitis and experimental allergic encephalomyelitis [78–80]. Patients with SLE, RA, Reiter’s and Sjögren’s syndromes have significantly elevated levels of prolactin [34–37]. Since AVP enhances prolactin secretion, enhanced AVP production in these diseases might play a part in the excessive and dysregulated secretion of prolactin, and thus be an additional susceptibility hormonal factor for the development of chronic inflammatory disease.

What would be the immunological consequences of enhanced AVP production? The primary immune response initially involves Th1 cellular activation followed by Th2 cell responses [81]. AVP and CRH are pro-inflammatory and can enhance Th1 cellular responses by augmenting IFN-γ and IL-2 production, respectively, in vitro. By contrast, corticosteroids suppress Th1 cells whilst upregulating Th2 cellular activity [82]. Thus, the high levels of circulating AVP and increased secretion of CRH into the inflamed joints of the Lewis rats associated with low circulating levels of corticosterone would potentiate Th1-mediated cellular responses, thus contributing to the pathophysiology of chronic inflammation [83–85]. A similar situation might exist in RA patients.

SUMMARY AND CONCLUSIONS

Our current understanding of the immune effects of AVP may be summarized as follows. AVP is involved in the regulation of ACTH secretion by the pituitary and, therefore, corticosteroids by the adrenal glands. It is involved in the inflammatory stress response and can modulate the fever response and generation of adaptive behaviour, and upregulates ACTH and prolactin production. The effects of inflammatory cytokines such as IL-1β, TNF-α and IL-6 on AVP secretion are controversial, but are generally thought to stimulate AVP release. AVP has direct effects on inflammatory cells exerted via AVP receptors that are expressed on these cells. These effects include the enhancement of IFN-γ and primary antibody production. Increased AVP production in Lewis rats is a susceptibility factor for developing chronic inflammatory disease. Invoking direct human implications is premature at the moment. However, since patients with RA share some of the neuroendocrine defects described in Lewis rats, it could be hypothesized that excessive and dysregulated production of AVP might be an additional neuroendocrine factor in the immunopathophysiology of the disease. Such a possibility is certainly worthy of investigation as it might open new therapeutic avenues.

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