Neuroendocrine markers in aging brain: Clinical and neurobiological significance of dexamethasone suppression test


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ABSTRACT. The dexamethasone suppression test (DST) is commonly accepted as an indicator of hypothalamus-pituitary-adrenal (HPA) axis functioning in clinical practice. In this study, DST was carried out in a geriatric population composed of patients with dementia of Alzheimer type (DAT), stroke and age-matched controls. The stress state of the subjects was also functionally assessed by the Symptoms Rating Test (SRT). The results disclosed no significant differences in basal cortisol levels in the three groups. A positive correlation between age and log-transformed basal cortisol levels was found in the entire population as well as in each group. After dexamethasone administration, 20% of controls, 49% of DAT patients, and 48% of stroke patients were non-suppressors. At 8.00 a.m. and 11.00 p.m. after dexamethasone, cortisol levels were significantly lower ($p < 0.02$) in controls than in pathological groups. A significant positive correlation between age and symptoms of depression and anxiety was found. One-third of stroke patients showing lesions in the right hemisphere were non-suppressors, and presented mostly subcortical infarcts, while 1/4 of them had depressive disorders. This study demonstrated a progressive increase in basal cortisol levels and depressive symptoms with age, a poor diagnostic value of DST in age-relat-ed pathological conditions such as DAT and stroke, and the role of these cerebral pathologies in amplifying the neuroendocrine dysregulation due to the ageing process itself. DST is a useful biological marker for disclosing the vulnerability of the ageing brain, but it has no diagnostic value.

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INTRODUCTION

In recent years many studies have been carried out and many hypotheses have been formulated to explain the biological bases of aging brain and related disorders. A particularly fascinating theory considers senescence a condition of decreased adaptability to stress, suggesting that the cause of age-related phenomena resides in the breakdown of the neuroendocrine system. In line with this, other authors (1) previously held that humans are born with a fixed quantity of “adaptive energy” which is progressively reduced along with repeated exposure to stressing factors.

The glucocorticoid hormones readily increase available energy by means of catabolic processes, and represent the final step of hypothalamic-pituitary-adrenal (HPA) axis activation after a stressor input. At each level of this axis,
several positive and negative feedback systems control the secretion of the hormones involved. Adrenal cortisol is the main stress hormone in humans, and pituitary ACTH is its main stimulating factor. Several polypeptide and monoamine factors in turn, control ACTH release; hypothalamic corticotropin-releasing factor (CRF), arginine-vasopressin (AVP), vasoactive intestinal peptide (VIP) or catecholamines have a stimulating effect while somatostatin and glucocorticoids inhibit ACTH secretion (2).

Undoubtedly, the central nervous system (CNS), the endocrine system and peripheral tissues are related in a very complex way. In this context, age-related phenomena, namely progressive neuronal loss, could contribute to an alteration in glucocorticoid release.

Target cells for glucocorticoids are more highly concentrated in the hippocampus than in any other brain region, which thus represents a major “control system” of HPA axis activity. Many experiments (3) clearly demonstrated both the hippocampal inhibitory influence on glucocorticoid secretion, and the possibility of hippocampal neuron injury through a state of hyperadrenocorticism leading to dysregulation of HPA axis activity.

In this perspective, an alteration in the neuroendocrine control mechanism might be an important pace-maker of the mammalian aging process: initial age-related alterations in brain synaptic function could lead to gradual changes in neural control of endocrine processes which, in turn, could provoke “cascading” functional imbalances and consequently age-related neuronal deterioration (4).

Many experiments have shown that elevated quantities of adrenocorticoids induced clinical alterations highly similar to the syndrome accompanying mammalian aging, and this suggests that neural and endocrine changes in the adrenal system are somehow related during aging (either as cause or effect). Other factors causing structural or functional brain alterations obviously may contribute to age-related cerebral changes, but the morphological modifications that take place following prolonged administration of high glucocorticoid doses are indicative of selective neuronal damage due to adrenal hormones.

In clinical practice, the dexamethasone suppression test (DST) is a useful method for studying HPA axis function. Administration of dexamethasone inhibits ACTH release, and consequently leads to a marked reduction in plasma cortisol levels; in subjects with HPA axis dysregulation, cortisol secretion is not suppressed, and the subject is defined an “escaper” or “non-suppressor”.

DST was primarily considered for its diagnostic utility in cases of endogenous depression. In fact, in patients with melancholia it showed a sensitivity of 67%, and specificity of 96% (5). This study was followed by many others in which DST was employed not only to assess depression but also other psychogeriatric pathological conditions, such as degenerative dementia, multi infarct dementia and confusional state (6-9), where an HPA axis dysregulation could be expected; high percentages of non-suppressor subjects were found, suggesting that the diagnostic value of DST decreases with age and age-related disorders.

Recent reports describe a depressive state frequently associated with cerebrovascular disease, especially after a stroke episode; this “post stroke depression” (PSD), found in up to 25% of the patients, would be related to the location of the brain infarct (10). In particular, major depression was significantly more frequent in patients with left anterior compared to right hemispheric lesions, and the proximity of the anterior border of the lesion to the frontal pole correlated significantly with the severity of depression. Other studies, however, did not confirm differences between right and left hemisphere lesions in the frequency of PSD (11). To better evaluate depression due to stroke, investigations were carried out in subjects with cerebral infarction (12, 13): it was found that over 50% of the patients showed an abnormal response to DST.

The aim of the present study was to contribute further to the understanding of the clinical significance of DST in geriatric subjects. To this end, patients with primary degenerative dementia, cerebrovascular disorders and age-matched controls were studied; the presence of psychopathological disturbances (anxiety, depression, somatic disorders and inadequacy) was also evaluated.