COGNITIVE FUNCTION AND BRAIN-ADRENAL AXIS ACTIVITY IN AGING, DEPRESSION AND DEMENTIA

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INTRODUCTION

The brain-adrenal axis* represents one of the major adaptation mechanisms maintaining the body homeostatic balance (see Dilman, 1971). Since the 1960s it has become an object of increased attention to psychiatrists and has resulted in the avalanche of publications reviewed elsewhere (Stokes, 1987). This chapter reviews the findings of our research team as well as closely related literature in an attempt to offer a satisfactory explanation of the known facts and to suggest directions for further investigation.

The starting point of our studies was the understanding that brain-adrenal axis activation (initially viewed as a specific feature of, at least, a subgroup of depressions) is a non-specific phenomenon in regard to any pathological entity (Dilman, 1971; Dilman et al., 1979; Stokes et al., 1984). Brain-adrenal axis activation reflects rather, some brain-endocrine changes that might occur in the course of normal aging (see Dilman et al., 1979) and pathological conditions (depression, see Carroll et al., 1981; alcohol withdrawal, see Oxenkrug, 1978; primary degenerative dementia, see Raskind et al., 1982). Such an approach does not exclude the evaluation of brain-adrenal activity as an additional laboratory test (Carroll et al., 1981). Fever, in the same vein is a non-specific phenomenon for pneumonia or appendicitis but rather points to the presence of inflammation and might be useful for diagnostic and follow-up purposes.

Normal aging. There is ample experimental evidence of brain-adrenal activation in the course of normal aging (DeKosky et al., 1984; Landfield et al., 1970, 1981; Oxenkrug et al., 1983). Some hypotheses (see Dilman et al., 1979; Landfield, 1986) suggest that brain-adrenal activation is one of the main mechanisms of normal aging. This suggestion is in line with the findings that chronic exposure of the young animal to elevated levels of corticosteroids caused hippocampal morphological changes typical

*"Brain-adrenal" seems to be a more appropriate definition than hypothalamic-pituitary adrenal (at least in the context of the current review) since some other brain structures (hippocampus: McEwen et al., 1975; pineal: Wurtman & Altshule, 1959; Oxenkrug et al., 1984) might contribute to the regulation of adrenal activity.
of old animals (see Landfield, 1986); inhibited the sprouting of hippocampal noradrenergic neurons (DeKosky et al., 1984) and down regulated hippocampal corticosterone receptors (Sapolsky & McEwan, 1986).

In contrast to abundant animal data, activation of the brain-adrenal axis in humans has not been well established until recently. The routine tool for the evaluation of brain-adrenal axis activity is dexamethasone (DEX) suppression test; the failure of DEX (a synthetic glucocorticoid) to suppress blood cortisol levels indicates an overactivation of brain-adrenal axis. The use of 1 mg of DEX failed to find an age effect on post-DEX cortisol levels partly because 1 mg of DEX resulted in almost complete suppression of cortisol levels (mostly <1 microg/dl) (Tourigny-Rivard et al., 1981). Recently, Rosenbaum et al. (1984) suggested that aging effect on post 1 mg of DEX cortisol levels might be revealed with the use of radio-immunoassay but not competitive protein binding methods of plasma cortisol determination. The use of 0.5 mg of DEX yields various degrees of cortisol suppression (from <1 to 5 microg/dl) and allows for the establishment of a positive correlation between plasma post-DEX cortisol levels and age in normal volunteers (Oxenkrug et al., 1983). These results were in line with the previously observed increase of post-prednisolone urine corticosteroid levels in normal aged subjects (see Dilman et al., 1979). The other tool for the evaluation of brain-adrenal axis activity is the determination of 24 h blood cortisol secretion. Positive correlation has been found in normal subjects between age and 24 h plasma cortisol levels (Halbreich et al., 1985). According to Halbreich et al. (1985) each decade of age results in 0.65 microg/dl increase of 24 h plasma cortisol. The use of only one-point (morning) plasma cortisol level fails to produce statistically significant correlation between basal plasma cortisol levels and age (Oxenkrug et al., 1983; Georgotas et al., 1986). However, linear regression analysis reveals the contribution of basal (pre-DEX) morning plasma cortisol levels to age-associated increase of post-DEX cortisol levels. The relationships between age, pre- and post-DEX plasma cortisol levels was described by the following equation (Branconnier, Oxenkrug et al., 1984):

\[
\text{PostDEX cortisol} = 0.12 \times (\text{preDEX cortisol}) + 0.04 \times (\text{age}) - 1.34
\]

The highest post-DEX cortisol levels (4 to 5 microg/dl) were observed among subjects older than 55 years suggesting that the use of one and the same normal value (cut-off at the level of 4 to 6 microg/dl) is inappropriate for elderly population, at least, with the 0.5 mg of DEX test. Theoretically, this equation might also be used for calculation of "age" based on determination of pre- and post DEX cortisol levels:

\[
\text{"Age"} = (\text{PostDEX cortisol} - 0.12 \times (\text{preDEX cortisol}) + 1.34):0.04
\]

The calculated "age" might reflect some (but not all) age-associated biological changes (mostly in brain-adrenal axis). Therefore, such a calculation might be used for the evaluation of the correspondence between brain-adrenal axis activity and chronological age of the subject studied.

Therefore, both animal and human data suggest the progressive activation of brain-adrenal axis during the course of normal aging.

The memory changes are nearly universal in aging. Although no data on the correlation between cognitive function and brain-adrenal axis activity during the course of the normal aging is available, one may suggest the existence of such a correlation considering that age associates with both brain-adrenal axis activation (Dilman et al., 1979; Oxenkrug et al., 1983) and cognitive impairment (see Branconnier and De Witt, 1984).

Cushing's and Down's Syndrome. Both syndromes are considered the