Available online at www.sciencedirect.com
ScienceDirect
Ageing Research Reviews 7 (2008) 225–233
ageing research reviews
www.elsevier.com/locate/arr

Review

Role of neuroendocrine pathways in cognitive decline during aging

Ettore Ferrari [a,*], Flavia Magri [b]

[a] Department of Internal Medicine and Medical Therapy, University of Pavia, Via Alboino 21, 27100 Pavia, Italy
[b] Department of Internal Medicine and Medical Therapy, I.R.C.C.S. "S. Maugeri" Foundation, University of Pavia, Italy

Received 22 December 2007; received in revised form 2 July 2008; accepted 2 July 2008

Abstract

The pineal and pituitary–adrenocortical secretions play an important role in adaptive responses of the organism acting as coordinating signals for both several biological rhythms and multiple neuroendocrine and metabolic functions.

The more relevant neuroendocrine changes occurring with ageing affect the secretion of melatonin and of corticosteroids. These changes may be clearly appreciated by the study of their circadian rhythmicity.

The circadian profile of plasma melatonin was clearly flattened in elderly subjects and even more in old individuals with dementia. Indeed, the impairment of melatonin signal occurring in aging was related either to age itself or to the cognitive performances of subjects.

The biosynthetic dissociation between glucocorticoids and androgen secretion is responsible for the selective impairment of androgens, such as DHEA and DHEA-S, by comparison to cortisol.

Due to the opposite effects of the two kinds of corticosteroids either in the periphery and in the CNS, the imbalance between glucocorticoids and androgens, well demonstrated by the evaluation of the cortisol/DHEA-S molar ratio, may be responsible for the occurrence in the CNS of a more neurotoxic steroidal milieu, already present in clinically healthy elderly subjects and especially in patients with dementia. The effects of that steroidal milieu are more prominent at the level of the hippocampal–limbic structure, involved both in the modulation of endocrine structures, such as the HPA axis, and in the control of cognitive, behavioral and affective functions.

Keywords: Aging; Senile dementia; Melatonin; HPA axis; Circadian rhythms

1. Background

The changes affecting the organism during physiological aging do not spare the main integrating systems, namely the central nervous system (CNS) and the endocrine system, which closely interact with each other in the maintenance of homeostasis. Indeed, aging is characterized by imbalances among the different central neurotransmitter pathways, with clear impairment of the noradrenergic and dopaminergic systems and relative maintenance of the serotonergic and cholinergic ones (Rehman and Masson, 2001).

On the whole, the neuroendocrine modifications occurring with aging seem to be related more to disordered relationships between neural and hormonal signals than to specific alterations of the various endocrine structures themselves.

The age-related modifications of the CNS, namely progressive neuronal loss and compensatory gliosis, are particularly pronounced at the level of the hippocampus, limbic system and hypothalamus, and hypothalamo-pituitary–adrenal axis (HPA).

The hippocampal formation is highly exposed to the neurotoxic effects of stress hormones, due to its high concentration of corticosteroid receptors. Since the hippocampus plays a central role in limiting stress-related HPA activation, the reduction of corticosteroid binding sites due to hippocampal damage results in abnormally persistent stress-induced HPA activation with consequent hypercortisolemia and impaired sensitivity to steroid feedback regulation (Herman et al., 2003).

It is well known that the brain glucocorticoid binding sites include two different types of intracellular receptors (Veldhuis et al., 1982; Reul and de Kloet, 1985): mineralocorticoid (MRs) and glucocorticoid receptors (GRs). The former, highly expressed in the

* Corresponding author. Tel.: +39 0382 302800; fax: +39 0382 533386.
E-mail address: ettofer33@tiscali.it (E. Ferrari).

1568-1637/$ – see front matter
doi:10.1016/j.arr.2008.07.001

hippocampal–limbic area, are characterized by a high affinity for glucocorticoids and are activated even by low basal cortisol levels. On the contrary, GRs have a widespread distribution in the brain, being present in the pituitary, prefrontal cortex and hypothalamus, thalamus, raphe area, and cortex (Reul and de Kloet, 1985), and they have a low glucocorticoid affinity; consequently, they are activated after the complete saturation of MRs and only by high steroid levels, corresponding to the crest-time of the circadian cortisol rhythm or to stress conditions (Meaney and Aitken, 1985; Diorio et al., 1993).

An imbalance between MR- and GR-mediated effects may by responsible for changes in the responsiveness of the HPA to excitatory stimulations (De Kloet, 1991).

According to the glucocorticoid cascade hypothesis advanced by Sapolsky et al. (1986), chronic exposure to glucocorticoid could down-regulate the central GRs, especially at hippocampal level, impairing HPA sensitivity to negative steroid feedback. This, in turn, would increase the neurotoxic potential of the steroid milieu and may be responsible for degenerative changes and neuronal loss. In animal models the extent of glucocorticoid hypersecretion is correlated with the severity of the degenerative modifications of the hippocampal neurons, which also become more vulnerable to metabolic and vascular challenges (Landfield et al., 1978; Sapolsky et al., 1985). The hippocampus is a crucial area for learning and memory, too, and plays a major role in many neuropsychiatric diseases (Herman et al., 2005). The association between HPA function and cognition is mediated by the involvement of the limbic system.

So-called long-term potentiation (LTP), a physiological correlate of the strength of synaptic communication, is related to MR/GR rate of occupancy. Synaptic plasticity, in the form of LTP, is affected by adrenal steroid manipulations; in particular, adrenal steroids exert a bimodal effect on LTP, MR activation enhancing and GR activation suppressing the phenomenon (Pavlides et al., 1996). Furthermore, a dose-dependent relationship between corticosteroids and memory process was found in animal models and explained by the differential activation (or blockade in the case of antagonist administration) of MRs and GRs, particularly at hippocampal level (De Kloet et al., 1999; Lupien and McEwen, 1997).

2. Hormones and cognition

2.1. Melatonin

Age-related changes in cognitive and affective performances have often been linked to an imbalance between pro-oxidant and antioxidant factors (LeBel and Bondy, 1992; Lass et al., 1998; Ames et al., 1993). However, while an association between oxidative events and their deleterious consequences on aging has been shown repeatedly, evidence of a causal relation between oxidative events and impaired neurological or behavioral status is less definitive.

Melatonin (*N*-acetyl-5-methoxytryptamine), a tryptophan metabolite synthesized mainly by the pineal gland, has several physiological functions; for example, it modulates circadian rhythms, clears free radicals, improves immunity, and generally inhibits the oxidation of biomolecules (Arendt, 1988).

Blood melatonin concentrations exhibit clear circadian fluctuations, being highest at night-time and lowest during the day. Therefore, the melatonin secretion represents a very robust biochemical signal of night.

The melatonin circadian rhythm is modulated by the hypothalamic suprachiasmatic nucleus (SCN), which is regarded as a ‘‘biological clock’’ for many other bioperiodic functions, too (Nishino et al., 1976; Rusak and Zucker, 1979). The SCN receives light stimuli through the retino-hypothalamic pathway and conveys signals to the pineal gland via the sympathetic cervical system. It is important to note that even if light inhibits melatonin secretion, the melatonin circadian rhythm, because of its endogenous origin, is preserved. Furthermore, melatonin can directly influence the CNS through complex feed-forward and feedback mechanisms with multiple and coordinated rhythmic interactions (Sanchez De La Pena et al., 1982; Milin et al., 1993) (Fig. 1). As example of feed-sideward it may be considered the chronomodulatory effect of pineal compounds on the adrenocortical glucocorticoid secretion, according to the circadian stage.

Noradrenalin, through its binding to the $\alpha 1$ and $\beta 1$ adrenergic receptors, is the main neurotransmitter involved in melatonin secretion. During light exposure, noradrenalin release is inhibited by hyperpolarization of the retinal photoreceptor cells (Fung, 1987); darkness, on the other hand, leads to activation of the same system and to increased melatonin secretion (Pangerl et al., 1990).

Melatonin is rapidly metabolized, especially by the liver, and excreted in urine. Indeed, urinary levels of 6-sulfatoxymelatonin (aMT6s), the main melatonin urinary metabolite, have been found to closely parallel plasma melatonin concentrations (Lynch et al., 1975).

The melatonin circadian rhythm becomes apparent after the second or third month of life, with melatonin production reaching the highest nocturnal levels in children aged 1–3 years. Thereafter, melatonin circadian fluctuations, although persisting, show two significant declines: the first at puberty and the second during the progression from adulthood to senescence (Lynch et al., 1975; Touitou et al., 1986; Cagnacci et al., 1995; Ferrari et al., 1995; Magri et al., 1997). A 40–50% reduction in the nocturnal rate of melatonin production has been calculated in elderly subjects (Touitou, 2001).

It is now generally accepted that melatonin deficiency is closely related to aging and age-related diseases (Arendt, 1988). Indeed, many properties of melatonin can be regarded as anti-aging or as aging-delaying; for example, melatonin acts directly as a scavenger of free radicals and indirectly as an activating factor of antioxidative defense systems (Reiter et al., 2001; Qi et al., 2001; Tan et al.,