Interdiscipl. Topics Geront., vol. 24, pp. 98–110 (Karger, Basel 1988)

Glucocorticoid Receptors, Stress and Aging

Ramesh Sharma[1], *Paola S. Timiras*

Department of Physiology-Anatomy, University of California, Berkeley, Calif., USA

Overview

What are the causes of the decreased ability to respond to stress in old age? One among many hypotheses focuses on the hypothalamopituitary-adrenal axis as a key regulator of homeostasis and adaptation; however, other organs, such as the lungs, kidneys, liver and gut are also involved. Maintenance of homeostasis involves a complex series of integrative functions in which almost all body organs and systems participate, albeit in varying degrees. Thus, homeostatic competence provides a 'panoramic view' of overall physiological performance and explains the current interest among physiologists to identify the control mechanisms involved in this integrated activity.

Under resting (basal) conditions few changes occur in hypothalamopituitary-adrenal function with increasing age. Similarly, fasting blood sugar levels remain constant throughout the life span and the blood acidity and bicarbonate content are closely regulated, even into advanced age. In contrast, the rate at which the body is able to readjust and return to normal resting values after the experimental alteration of blood sugar, bicarbonate, or a stress situation stimulating adrenal response is much slower in old subjects than in young. As functional performance declines with increasing age and as pathological events accumulate and become more severe, the capacity of the organism to synchronize defensive and homeostatic mechanisms is concomitantly impaired. Thus, the failure of the elderly to adapt

[1] Ramesh Sharma offers thanks to the Ministry of Human Resources and Development, Government of India for the National Scholarship and the University of Manipur for the study leave.

to internal and external environmental changes reflects more the inability to purposefully coordinate several functions involved in supporting homeostasis than the failure of any single function (although the failure of one may provide a trigger) [1, 2].

Evidence of decreased resistance to environmental changes accompanying the aging process is plentiful and the increased risk of death following stress in the elderly is acknowledged. Older people are less resistant than younger subjects to excessively cold or warm temperatures due to the progressive deterioration of thermoregulatory mechanisms. Equally diminished is the capacity to adapt to hypoxia, traumatic injury, exercise, and physical work, all types of stress that require complex physiological adjustments. For example, the ability to carry out physical work involves competence of numerous functions, such as oxygen uptake by the lungs and/or tissues, pulmonary ventilation, diffusing capacity of lungs, cardiac work, pulse rate, and production and elimination of blood lactate. Alteration in any of these factors or their interrelation will result in a marked decrease in work capacity and a significant increase in the time for recovery from exercise. Emotional stress in the old may also trigger or aggravate a series of physical ailments that, superimposed on an already debilitated state, would lead to disease and death.

Some of the aging changes of the adrenal cortex and medulla and those in the nervous system may be responsible for the decline in adaptive capability. Stressful stimuli activate both the hypothalamopituitary-adrenocortical and sympathoadrenal systems which coordinate physiological reactions to maintain homeostasis. This coordination is through a series of neuroendocrine signals which involve various hormones and brain centers. Aging disrupts the synchrony of these signals: the capacity to restore the original homeostasis is altered and the hypothalamus is unable to undergo the major remodeling of its circuitry necessary for adaptation [3].

The role of the hypothalamopituitary-adrenal system in adaptive responses was first emphasized by Cannon [4] for the adrenal medulla and by Selye and Prioreschi [5] for the adrenal cortex. This role has been both supported and criticized by many investigators and continues to be controversial. However, only recently have advances in neuroendocrinologic knowledge and techniques established more solid cellular and molecular bases for these views. For example, at the cellular level, abnormalities of protein metabolism with stress have been implicated as contributing to the degenerative changes leading to the pathology of dementias; at the molecular level, loss of glucocorticoid receptors in selected brain neurons may

release the hypothalamopituitary-adrenocortical system from the inhibitory action of limbic structures with consequent failure to adapt [6]. We shall be considering in this review the relationship between glucocorticoid receptors, stress and aging.

Glucocorticoid Receptors – Regional Distribution and Characteristics

Glucocorticoids such as cortisol and corticosterone have a multitude of effects within the body. They generate appropriate physiological (metabolic) adjustments necessary for the responses to stress [7]. The major effects of glucocorticoids, in response to stress and environmental insults, are to reduce inflammation, stabilize blood glucose, maintain muscle strength, and promote fluid excretion. These hormones are secreted from the adrenal cortices under the control of the brain via pituitary, hypothalamus and limbic system. Various environmental and psychological stimuli activate the release of corticotropin-releasing hormone (CRH) from the hypothalamus, CRH in turn stimulates the pituitary adrenocorticotropic hormone (ACTH) which regulates the secretion of glucocorticoids from the adrenal gland [8]. Glucocorticoids are involved in defense mechanisms to stress, both at central and peripheral levels. These effects, turning on and off of the adrenal-pituitary axis are mediated through pituitary, hypothalamus and limbic brain regions (fig. 1).

The glucocorticoid receptors are located in most target tissues. High-affinity glucocorticoid receptors have been demonstrated in different brain regions [9–11]. The highest concentrations of glucocorticoid receptors are present in the hippocampus (fig. 2). Due to the presence of high level of glucocorticoid receptors, the hippocampus is believed to be a mediator of glucocorticoid effects on the brain. It is referred to as a 'window' through which glucocorticoids modulate such complex activities of central nervous system (CNS) as mood, motivation and learned behaviors [12]. The presence of glucocorticoid receptors in CNS supports the role of glucocorticoids in switching on and off the stress responses through negative feedback [13]. Glucocorticoid effects on the brain are highly diversified: they influence monoamines, neuropeptides and amino acid transmitters at the molecular level, induce cell loss at the cellular level, increase excitability and altered behavior at the functional level. These functional, cellular and molecular changes occur throughout development, adulthood and aging of organisms.

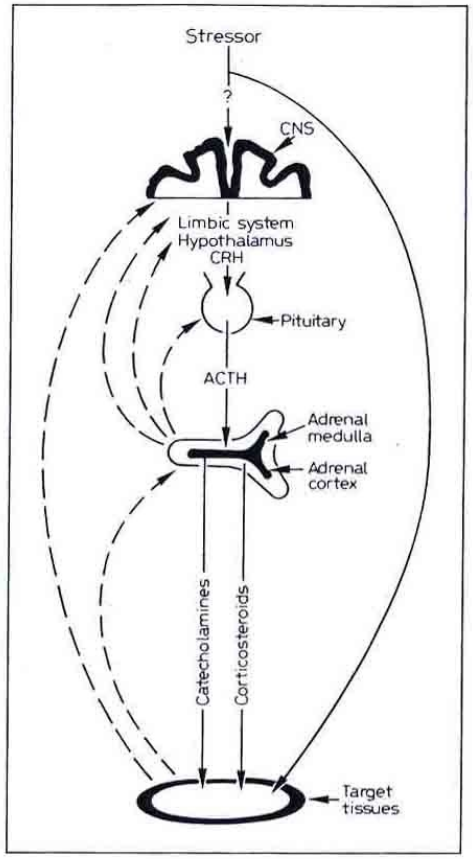

Fig. 1. Schematic representation of the postulated mechanisms of stressors on target tissues. Stressors act on the higher central nervous system (CNS) centers through mechanisms still unknown (?). Stressors may also act directly on the target tissues. Stimulation of CNS centers is relayed to the limbic system, particularly the hippocampus and from there to the hypothalamus. In the hypothalamus, synthesis and release of CRH are increased and the hormone through the portal system stimulates the anterior pituitary to increase ACTH production. ACTH, in turn, stimulates the adrenal cortex to produce more corticosteroids, which then act on target tissues. Simultaneously with the activation of the hypothalamopituitary-adrenal axis, there is also a sympathetic activation of catecholamine release from the adrenal medulla. The overall responsiveness of this complex neuroendocrine system to stressors also depends on the presence of negative feedbacks (---). Such feedbacks exist between steroid-pituitary, steroid-hypothalamus and steroid-limbic systems. The responses of target tissues may also be modulated by negative feedbacks either directly on the adrenal or CNS.

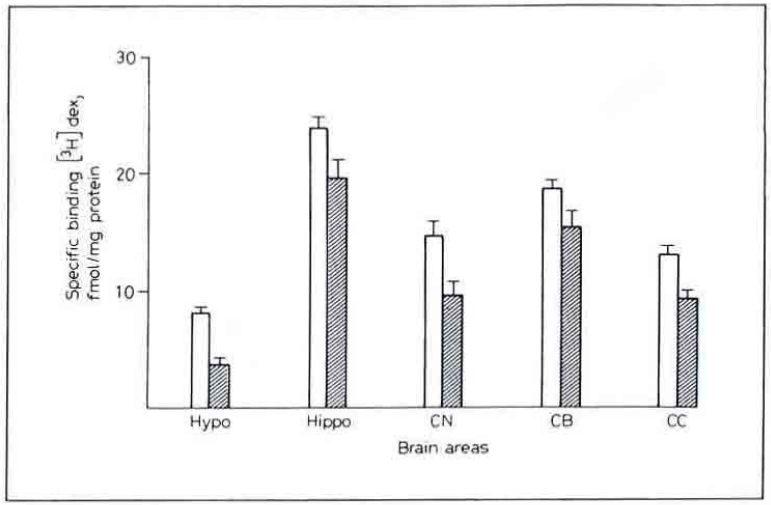

Fig. 2. Saturable cytosolic-specific binding of [^{3}H]dexamethasone ([^{3}H]dex) in hypothalamus (Hypo), hippocampus (Hippo), caudate nucleus (CN), cerebellum (CB) and cerebral cortex (CC) of 3- (□) and 26-week-old (▨) adrenalectomized Long-Evans male rats. Results are mean ± SD of the 4–5 samples collected from 4–5 rats of each age group. Note that at both ages the number of binding sites is highest in the hippocampus. The binding sites decrease with age (20–30%) in all the brain areas [38].

In vitro binding studies have revealed at least two classes of corticosteroid receptors: type 1 (mineralocorticoids) and type 2 (glucocorticoids). They differ in affinity (K_d) and specificity for certain synthetic and naturally occurring corticosteroids [10]. The physical characteristics of neural glucocorticoid receptors have been examined in several studies. Using [^{3}H]dexamethasone, a synthetic glucocorticoid, as a ligand, most investigators have reported equilibrium dissociation constant (K_d) of 2–10 n*M* [14–16] and sedimentation coefficient of 6–8 S depending on the experimental conditions [14, 15]. Isoelectric focusing studies have demonstrated the existence of a single class of dexamethasone receptors with a pI of 6.1 [15, 16]. Brain glucocorticoid receptors display most of the kinetic properties similar to those of the receptors present in other tissues such as liver, kidney and thymus [11]. These intracellular receptors upon binding to hormones are activated prior to binding to nuclear acceptor sites. The activation of steroid-receptor complexes has been described as a not well-

defined, conformational change which enables the complexes to interact with specific acceptor sites on chromatin and modulate gene expression [17]. This nuclear binding capacity can be achieved in vitro by incubating the hormone-receptor complexes at 25 °C [18, 19] and under high ionic conditions [20]. Such phenomena are achieved possibly by exposure of positively changed amino acid residues on the surface of the receptor molecule, which in turn enhances the affinity for nuclei and polyanions such as DNA and DNA-cellulose [21]. The activation of glucocorticoid receptors occurs in vivo under physiological conditions and is thought to be rate-limiting for nuclear binding [22, 23].

Changes in Glucocorticoid Receptors during Development: Correlations with Adaptive Responsiveness to Stress

Adaptive responses to hormones are age-related phenomena as are changes in induction of many enzymes [24]. These hormone-mediated responses are controlled by binding of the hormone to specific intracellular receptors, by activation of hormone receptor complexes and interaction of these complexes to nuclear acceptor sites. Many of these events are altered with age [25, 26]. In the rat brain, glucocorticoid receptors are detectable as early as the 17th day of gestation. After birth, the receptor binding capacity gradually increases to adult levels by 15–30 days of age [27–29]; it also undergoes changes in physicochemical properties [26, 30, 31], which may account, at least in part, for changes with age in tissue responsiveness to glucocorticoids [32]. For example, nuclear transfer of bound hormone receptor complexes reaches mature levels only after the postnatal day 10 in the pituitary of rats. The reduced transfer of hormone receptor complexes to nuclei is correlated with the nonresponsive period to stress in neonatal rats [33]. We have observed a reduced heat activation of [^{3}H]-dexamethasone receptor complexes in the cerebral hemispheres of adult rats as compared to weanling rats [34].

The postnatal rise in the brain glucocorticoid receptors of rats during the 2nd week of life has been correlated with a low adrenocortical response to stress [35]. This period of adrenocortical unresponsiveness has been termed a 'stress-nonresponsive period'. The neonatal rats are less sensitive not only to the stimulatory effects of stress, but also to the inhibitory effects of circulating corticosterone. Administration of dexamethasone does not suppress circulating corticosterone titers in neonates, while it

does in adult rats [35]. In adult animals both corticosterone and dexamethasone inhibit subsequent adrenocortical secretion. The stress nonresponsive period has shown adaptive value on the development of central nervous system since high or low levels of corticosteroids are associated with abnormal neural and behavioral growth. The neonatal adrenocortical activity corresponds to the unique pattern of glucocorticoid receptor concentrations that exist in the brain and pituitary at these phases of the life span: this low, stable corticoid level appears suitable for neuronal development in glucocorticoid-sensitive brain regions [35].

Changes in Glucocorticoid Receptors during Aging: Correlations with Adaptive Responsiveness to Stress

Glucocorticoid binding sites have been reported to decline in the cerebral hemispheres of aged (24 months) rats [36], and in isolated neuronal perikarya from the cerebral cortex of aged Sprague-Dawley rats as compared to young rats [37]. [^{3}H]dexamethasone binding sites decrease by 20–30% in different brain regions of adult male Long-Evans rats as compared to weanling rats (fig. 2) [38]. In contrast, in C57/6J mice, the corticosterone binding sites in the cytosol of hypothalamus, hippocampus or cortex remain unchanged with senescence [39]. Likewise, the number of glucocorticoid binding sites was low in the hippocampus but not in other cortical brain regions of older rats [40]. A site-specific decrease in corticosterone binding was observed in the brain of aged rats [41]. In these studies, age-dependent decrease in receptors were marked in the hippocampus and amygdala but not in the hypothalamus, cortex and midbrain. These authors further established that the reduction in hippocampal receptors was due to decreased number of corticosterone-concentrating neurons as determined by autoradiography [42]. Glial and other cell uptake of [^{3}H]-dexamethasone was not depressed in aging hippocampus [41]. The loss of hippocampal glucocorticoid receptors has been well correlated with the loss of hippocampal neuronal population in discrete subfields of Ammon's horn as a function of age [6]. These neuronal losses in aged animals have been associated with the increased glucocorticoids with age as demonstrated first in the hippocampus of guinea pigs [43]. Daily subcutaneous injection of corticosterone over 3 months led to loss of [^{3}H]dexamethasone receptor binding sites in vitro and neuronal loss in specific areas of Ammon's horn [6]. The regulation of brain corticosteroid receptors during

aging seems to be a multifactorial process. The levels of glucocorticoid binding sites in neural tissues are controlled by several factors in addition to age. These factors include neural innervation [44], neurotransmitter activities [45, 46], and various other integrating hormonal systems [47–49].

Various types of stress such as cold and hot exposures, social crowding and handling, as well as age and a diabetic condition may lead to a reduced number of receptors for adrenal steroids in hippocampus. A common factor in these conditions is the persistent elevation of corticosterone in the circulation [11]. There is a downregulation of glucocorticoid receptors with the elevated level of corticosterone [6]. The regulation of corticosterone receptors shows a biphasic increase with adrenalectomy. In the first 12–18 h after bilateral adrenalectomy, the rise is mainly due to clearance of endogenous hormone. The second phase takes a number of days to develop fully and represents an increase in total receptor numbers [50]. The initial increase in binding sites is relatively constant for 3–4 days postadrenalectomy. Binding then rises up to 30 days when it returns to 3-day level and finally falls still further when measured 180 days after the operation [51]. The number of hippocampal glucocorticoid binding sites is reduced by injecting corticosterone into adrenalectomized rats [52].

Brain glucocorticoid receptors also respond to chronic stress-induced elevations of circulating corticosteroids [53]. Repeated stress over 3 weeks decreases the number of cytosolic receptors in the hippocampus. This up- and downregulation of glucocorticoid receptors in some brain regions and pituitary is thought to be governed not only by corticosteroids but also by certain neuropeptides such as vasopressin and ACTH [46, 49].

By the 14th postoperative day, hypophysectomy increases the retention of labeled corticosterone by nuclei of in vivo cells more than adrenalectomy. Cytosolic [^{3}H]corticosterone binding at 14 days is also higher in the hippocampus, hypothalamus, and septum of hypophysectomized rats. This binding is reversible by systemic administration of corticosterone and ACTH [46].

A main action of glucocorticoids on the brain and pituitary is to govern the production and secretion of hormones of the hypothalamic-pituitary-adrenal axis [11]. The feedback actions of adrenal steroids have been categorized into three groups: fast, intermediate, and slow [13]. The first category involves the direct actions of glucocorticoids on the membranes, independent of RNA and protein synthesis, to change blood steroid levels. The second category involves actions of glucocorticoids which influence

RNA and protein synthesis and which regulate gene expression related to cellular and metabolic events. The third category involves actions of glucocorticoids that suppress the synthesis of CRH, vasopressin and ACTH; these actions also involve RNA and protein synthesis and are responsible for the negative feedback of glucocorticoids on hypothalamus and pituitary [13].

The negative feedback actions of glucocorticoids affect not only the hypothalamus and pituitary but also the hippocampus, amygdala, septum and midbrain. For example, ablation of dorsal hippocampus reduces the effectiveness of dexamethasone in inhibiting basal and stress-induced pituitary-adrenal responses [54]. Because the stress response is lowered when hippocampal neurons are irreversibly lost and also by reduction in number of hippocampal corticosterone receptors [55], the hippocampus is thought to be a site for negative feedback by corticosterone in shutdown of the stress response. This reduction in receptor numbers is very specific for the hippocampus and does not occur in pituitary, hypothalamus, amygdala or septum, and restoration of normal receptor levels leads to reversal of the stress shutoff. However, in case of aging rats, the receptor deficit is due to neuronal loss [48].

The exact mechanism of hippocampal neurotoxicity by glucocorticoids is not well understood. It appears that age-related loss of hippocampal neurons is caused by cumulative exposure to basal titers of the steroid and that prolonged stress can accelerate such hippocampal aging [56]. Glucocorticoids have long been recognized for their potent catabolic effects on target tissues which include inhibition of glucose uptake, cell division, protein synthesis, as well as depletion of glycogen and triglycerides [7]. Thus, cumulative exposure to glucocorticoids as a function of age may ultimately prove sufficiently catabolic to directly destroy hippocampal neurons. On the other hand, glucocorticoid-induced neuronal loss may also occur in conjunction with other metabolic challenges with aging.

There are several pathological repercussions of the corticosterone hypersecretion in the aged rats. Most severe is the progressive loss of hippocampal neurons with prolonged exposure to corticosterone. This neuronal loss appears to accelerate further corticosterone secretion and shows a feed forward cascade with age. This would enhance the neuronal degeneration in the hippocampus and lead to hyperadrenocorticism [6]. Another consequence may be the reduced sprouting of axons. This phenomenon is produced in younger rats by maintaining corticosterone at high levels [57]. Elevated cortisone levels apparently have more widespread consequences

outside of the brain. For example, stress induces tumor growth in both young and old rats [58] but with increased incidence in the aged rats. This may in part be due to higher glucocorticoid levels in aged rats [58]. Also, glucocorticoid increase may be a causative factor in immunosuppression, hypertension, osteoporosis and steroid diabetes with advancing age [7].

Conclusions

The brain possesses receptors for adrenal glucocorticoids which change in number and some physicochemical properties during development and aging. Glucocorticoids affect several neurochemical reactions within the brain, including monoamines, amino acid transmitters, and some neuropeptides such as CRH, vasopressin, and ACTH. Their biochemical effects include regulation of neurotransmitter receptor levels, production of second messengers, and induction of several enzymes. Efficient functioning of the hypothalamic-pituitary-adrenal axis appears to be essential for adrenocortical stress reponses on and off. In general, the efficiency of this axis becomes reduced as a function of age, which may lead to decreased adaptive response in aged animals. Repeated exposure to various kinds of stresses throughout the life span induces alterations which depend on age and target tissue. These alterations may disrupt appropriate articulation and timing of the necessary signals for an optimal hypothalamic-pituitary-adrenocortical function and thereby prevent efficient adjustments to internal and external demands as a function of age.

References

1 Timiras, P.S.: Physiology of ageing: aspects of neuroendocrine regulation; in Pathy, Principles and practice of geriatric medicine (Wiley, Chichester 1985).
2 Finch, C.E.; Landfield, P.W.: Neuroendocrine and autonomic functions in aging mammals; in Finch, Schneider, Handbook of the biology of aging; 2nd ed. (Van Nostrand & Reinhold, New York 1985).
3 Meites, J.: Changes in hypothalamic regulation of pituitary function in aging rats; in Enna, Samorajski, Beer, Brain neurotransmitters and receptors and aging and age-related disorders (Raven Press, New York 1981).
4 Cannon, W.G.: Organization of physiological homeostasis. Physiol. Rev. 9: 399–431 (1929).
5 Selye, M.; Prioreschi, P.: Stress theory of aging; in Shock, Aging – some social and biological aspects (American Association of Advanced Science, Washington 1960).

6 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.: The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. *7:* 284–301 (1986).
7 Munck, A.; Guyre, P.M.; Holbrook, N.J.: Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr. Rev. *5:* 25–44 (1984).
8 Makara, G.B.: Mechanisms by which stressful stimuli activate the pituitary-adrenal system. Fed. Proc. *44:* 149–153 (1985).
9 McEwen, B.S.: Glucocorticoids and hippocampus: receptors in search of a function; in Ganten, Pfaff, Current topics in neuroendocrinology, pp. 1–22 (Springer, Berlin 1982).
10 Meyer, J.S.: Biochemical effects of corticosteroids in neural tissues. Physiol. Rev. *65:* 946–1020 (1985).
11 McEwen, B.S.; Kloet, E.R.; Rostene, W.: Adrenal steroid receptors and actions in the nervous system. Physiol. Rev. *66:* 1121–1188 (1986).
12 Nakajima, S.: Hippocampal protein synthesis and spike discharges in relation to memory; in Isaacson, Pribram, The hippocampus vol. 1, pp. 393–413 (Plenum Press, New York 1975).
13 Keller-Wood, M.E.; Dallman, M.F.: Corticosteroid inhibition of ACTH secretion. Endocr. Rev. *5:* 1–24 (1984).
14 Alexis, M.N.; Stylianopoulou, F.; Kitraki, E.; Sekeris, C.E.: The distribution and properties of the glucocorticoid receptor from the rat brain and pituitary. J. biol. Chem. *258:* 4710–4714 (1983).
15 Meyer, J.S.; McEwen, B.S.: Evidence for glucocorticoid target cells in the rat optic nerve. Physicochemical characterization of cytosol binding sites. J. Neurochem. *39:* 435–442 (1982).
16 Clark, C.R.; MacLusky, N.J.; Naftolin, F.: Glucocorticoid receptors in the spinal cord. Brain Res. *217:* 412–415 (1981).
17 Yamamoto, K.R.A.: Steroid receptor regulated transcription of specific genes and gene networks. A. Rev. Genet. *19:* 209–252 (1985).
18 Kalimi, M.; Beato, M.; Feigelson, P.: Interaction of glucocorticoids with rat liver nuclei. I. Role of cytosol proteins. Biochemistry *12:* 3365–3371 (1973).
19 Milgrom, E.; Atger, M.; Baulieu, E.E.: Audiophilic activation of steroid hormone receptors, Biochemistry *12:* 5198–5205 (1973).
20 Bailly, A.; Savouret, J.F.; Sallas, N.; Milgrom, E.: Factors modifying the equilibrium between activated and non-activated forms of steroid-receptor complexes. Eur. J. Biochem. *88:* 623–632 (1978).
21 Disorbo, D.M.; Phelps, D.S.; Litwack, G.: Chemical probes of amino acid residues affect the active sites of the glucocorticoid receptors. Endocrinology *106:* 922–929 (1980).
22 Munck, A.; Foley, R.: Activation of steroid hormone-receptor complexes in intact target cells in physiological conditions. Nature *278:* 752–754 (1979).
23 Markovic, R.D.; Litwack, G.: Activation of liver and kidney glucocorticoid-receptor complexes occurs in vivo. Archs Biochem. Biophys. *202:* 374–379 (1980).
24 Kanungo, M.S.: Changes in enzymes during ageing; in Biochemistry of ageing, pp. 79–126 (Academic Press, London 1980).
25 Roth, G.S.; Hess, G.: Changes in the mechanisms of hormone and neurotransmitter action during aging: current status of the role of receptor and post-receptor alterations. Mech. Age. Dev. *20:* 175–194 (1982).
26 Kalimi, M.: Glucocorticoid receptors: from development to aging. A review. Mech. Age. Dev. *24:* 129–138 (1984).
27 Olpe, H.R.; McEwen, B.S.: Glucocorticoid binding to receptor-like proteins in rat brains and pituitary: ontogenetic and experimentally induced changes. Brain Res. *105:* 121–128 (1976).
28 Clayton, C.J.; Grosser, R.I.; Stevens, W.: The ontogeny of corticosterone and dexamethasone receptors in rat brain. Brain Res. *134:* 445–453 (1977).
29 Kitraki, E.; Alexis, M.N.; Stylianopoulou, F.: Glucocorticoid receptors in developing rat brain and liver. J. Steroid Biochem. *20:* 263–269 (1984).
30 Sharma, R.; Timiras, P.S.: Regulatory changes in glucocorticoid receptors in the skeletal muscle of immature and mature male rats. Mech. Age. Dev. *37:* 248–256 (1987).
31 Sharma, R.; Timiras, P.S.: Age-dependent regulation of glucocorticoid receptors in the liver of male rats. Biochim. biophys. Acta (in press).
32 Salky, M.; Koch, B.: Physicochemical analysis of glucocorticoid receptors in the immature pituitary gland: evidence for lability and aggregation of the heat-activated form. Mol. cell. Endocrinol. *28:* 27–35 (1982).
33 Salky, M.; Koch, B.: Ontogenesis of glucocorticoid receptors in anterior pituitary gland: transient dissociation among cytosolic receptor density, nuclear uptake and regulation of corticotropic activity. Endocrinology *108:* 591–596 (1981).
34 Sharma, R.; Timiras, P.S.: Activation of glucocorticoid receptors in the cerebral hemispheres of weanling and adult male rats. INS-ASN Joint Meet. Neurochem., La Guaira 1987).
35 Sapolsky, R.M.; Meaney, M.J.: Maturation of the adrenocortical stress response: neuroendocrine control mechanisms and the stress hyporesponsive period. Brain Res. Rev. *11:* 65–76 (1986).
36 Roth, G.S.: Age-related changes in specific glucocorticoid binding by steroid-responsive tissues of rats. Endocrinology *94:* 82–90 (1974).
37 Roth, G.S.: Reduced glucocorticoid binding site concentration in cortical neuronal perikarya from senescent rats. Brain Res. *107:* 345–354 (1976).
38 Sharma, R.; Timiras, P.S.: Changes in glucocorticoid receptors in different regions of brain of immature and mature male rats. Biochem. int. *13:* 609–614 (1986).
39 Neuben, J.; Holinka, C.; Latham, K.; Allen, J.; Finch, C.: Corticosterone binding in cytosols from brain regions of mature and senescent male C57BL/6J mice. Brain. Res. *115:* 345–351 (1976).
40 Defoire, C.; Turner, B.: Glucocorticoid binding is decreased in hippocampus but not cortex of aged rats. Abstr. Soc. Neurosci. *7:* 947 (1981).
41 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.: Corticosterone receptors decline in a site-specific manner in the aged rat brain. Brain Res. *289:* 235–240 (1983).
42 Meaney, M.J.; Sapolsky, R.M.; McEwen, B.S.: The development of the glucocorticoid receptor system in the rat limbic brain. II. An autoradiographic study. Devl. Brain Res. *18:* 165–168 (1985).
43 Muhlen, K.A.A.D.; Ockenfels, H.: Morphologische Veränderungen im Diencephalon und Telencephalon: Störungen des Regelkreises Adenohypophysennebennierenrinde. Z. Zellforsch. mikrosk. Anat. *93:* 126–141 (1969).

44 Nyakas, C.; Dekloet, E.R.; Veldhuis, M.D.; Bohus, B.: Corticosterone binding capacity increases in contralateral hippocampus after partial unilateral hippocampectomy. Neurosci. Lett. *21:* 339–343 (1981).
45 Valery, P.; Palmery, M.; Patacchioli, F.R.; Catalani, A.; Tita, B.; Angelucci, L.: Role and regulation of brain glucocorticoid receptors. Pharmacol. Res. Commun. *12:* 283–292 (1980).
46 Veldhuis, M.D.; Dekloet, E.R.: Significance of ACTH (4–10) in the control of hippocampal corticosterone receptor capacity of hypophysectomized rats. Neuroendocrinology *34:* 374–380 (1982).
47 Fridman, O.; Foglia, V.G.; DeNicola, A.F.: Reduction of [^{3}H]corticosterone binding to cytoplasmic receptors in the brain of diabetic rats. J. Steroid Biochem. *9:* 609–614 (1978).
48 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.; Rainbow, T.C.: Do vasopressin-related peptides induce hippocampal corticosterone receptors? Implications for Aging. J. Neurosci. *4:* 1479–1485 (1984).
49 Veldhuis, M.D.; Dekloet, E.R.: Vasopressin-related peptides increase the hippocampal corticosterone receptor capacity of diabetes insipidus (Brattleboro rat). Endocrinology *110:* 153–157 (1982).
50 McEwen, B.S.; Wallach, G.; Magnus, C.: Corticosterone binding to hippocampus: immediate and delayed influences of the absence of adrenal secretion. Brain Res. *70:* 321–334 (1974).
51 Stevens, W.; Reed, D.J.; Grosser, B.I.: Binding of natural and synthetic glucocorticoids in rat brain. J. Steroid Biochem. *6:* 521–527 (1975).
52 Tornello, S.; Orti, E.; DeNicola, A.F.; Rainbow, T.C.; McEwen, B.S.: Regulation of glucocorticoid receptors in brain by corticosterone treatment of adrenalectomized rats. Neuroendocrinology *35:* 411–417 (1982).
53 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.: Stress down-regulates corticosterone receptors in a site specific manner in the brain. Endocrinology *114:* 287–292 (1984).
54 Feldman, S.; Conforti, N.: Participation of the dorsal hippocampus in the glucocorticoid feedback effect on adrenocortical activity. Neuroendocrinology *30:* 52–55 (1980).
55 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.: Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc. natn. Acad. Sci. USA *81:* 6174–6177 (1984).
56 Sapolsky, R.M.; Krey, L.C.; McEwen, B.S.: The adrenocortical stress response in the aged male rat: impairment of recovery from stress. Exp. Gerontol. *18:* 55–63 (1983).
57 Dekosky, S.T.; Scheff, S.W.; Cotman, C.W.: Elevated corticosterone levels. A possible cause of reduced axon sprouting in aged animals. Neuroendocrinology *38:* 33–38 (1984).
58 Sapolsky, R.M.; Donnelly, T.M.: Vulnerability to stress-induced tumor growth increases with age in rats: role of glucocorticoids. Endocrinology *117:* 662–666 (1985).

Dr. Paola S. Timiras, Department of Physiology-Anatomy,
University of California, Berkeley, CA 94720 (USA)