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The glucocorticoid hormone: from pedestal to dust and back

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Abstract

A potential injury to the hippocampus has been postulated by the "glucocorticoid cascade hypothesis" as deriving from the life-long exposure to the stress glucocorticoid hormone. This hypothesis has been extensively resorted to in the search of a physio-pathological basis of the cognitive and behavioural impairments of old age, as well as for assigning to the hormone a not-irrelevant pathogenic role in brain degenerative diseases. Here I discuss the experimental evidences that have credited to stress a killing-licence, and pose, on the contrary, that the modest degrees of hypercortisolemia present in the above conditions could be interpreted as a beneficial occurrence.

Keywords: Stress; Glucocorticoid; Cytokine; Ageing; Alzheimer's disease

1. History

The concept of stress as a true physiological mechanism instrumental to the maintenance or recovery of homeostasis in the face of disturbing stimuli originated from Hans Selye's penetrating clinical and experimental observation of body's responses that are "unspecific" in nature and commonly associated with responses "specific" to any pathological stimuli — later defined as stressors. This concept, however, was not unequivocally derivable from the main source of the thinking of Selye (1950), "The Physiology and Pathology of Exposure to STRESS, A treatise based on the concepts of the GENERAL ADAPTATION SYNDROME and the DISEASE OF ADAPTATION". In fact, the image of "stress" that opens the volume and is reproduced in Fig. 1, purely representing intense suffering, contrasts radically with the dedication that reads: "...I CANNOT, AND SHOULD NOT, BE CURED OF MY STRESS BUT MERELY TAUGHT TO ENJOY IT."

Selye had not overlooked the great nervous–neuroendocrine multihormonal complexity of the stress response, whose clarification had to await more detailed biological knowledge. His singling out of the adrenal hormones as the final operant of the adaptive mechanism was a stroke of brilliance. This notion became so well established that, during the Second World War, the Germans were believed to be buying adrenal glands from Argentine slaughterhouses and using adrenal extracts from them to help their pilots fly at high altitudes. The rumour was a false one but it did lead to intensified study. By 1943, no less than 23 corticosteroids, among them the mineralcorticoids and the two main glucocorticoid hormones, corticosterone and hydrocortisone, had been isolated. In 1950, the achievement was honoured by the award of the Nobel Prize for Medicine or Physiology shared by Kendall, Hench and Reichstein. However, as early as in 1949, before the cytokine era, Selye had predicted the anti-inflammatory role of endogenous adrenocorticotropic hormone (ACTH) and cortisone, the "adaptive hormones", while emphasising the near-psychotic effects of the exogenous hormones in predisposed individuals. The great therapeutic value of appropriate doses of glucocorticoid hormone, as well as the mind-altering ability of excessive treatment and the ability to induce tolerance and dependence, were popularised as a result of Nicholas Ray's 1956 four-star film "Bigger Than Life". In the subsequent 20 years — the pedestal stage — the natural glucocorticoid gained acceptability in the field of hormonal therapy and psychoneuroendocrinology. During this stage, awareness grew of the complexity of the stress

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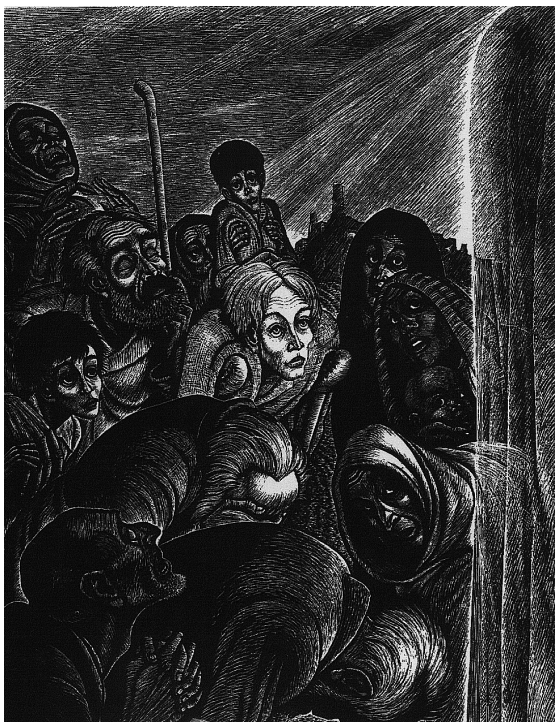


Fig. 1. Relief from stress (from a wood engraving "The Light" by Fritz Eichenberg).

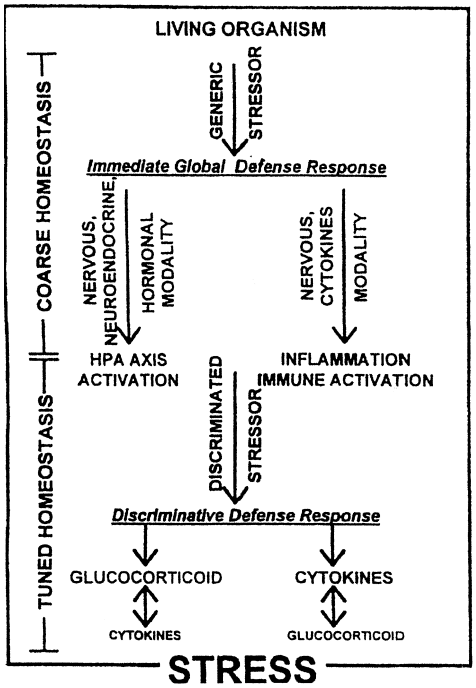


Fig. 2. The tuning of the stress circuit to the nature of the stressor.

phenomenon, particularly when adrenocorticoid receptors were found in the brain (McEwen et al., 1968). The work in the Rudolf Magnus Institute, leading to the biochemical and functional distinction between endocrine and behavioural regulation operated by two types of receptors, the glucocorticoid and the mineralcorticoid (Bohus and De Kloet, 1981; De Kloet et al., 1987), and to the identification of a peptidergic component, the pituitary peptides, from the fragmentation of β-endorphin and ACTH (De Wied, 1969), contributed to this recognition. At this point, the concept of stress could be defined as the condition, for all forms of life aimed at the preservation of the individual's life, compounded of the perturbation of the steady state and the organism's acute homeostatic repair response to the modifying agent — the stressor — or the organism's chronic adaptive resistance to it; without stress no evolution could have taken place. In all vertebrates, stress is a neuro-immuno-endocrine reverberating circuit, as schematised in Fig. 2, characterised by activation of the pituitary–adrenal axis and of the cytokine system through the vigilance of the brain, an adaptation mechanism that can pass from the physiological to the pathological when worked to excesses.

However, the finding in the 1980s that ageing animals could have increased levels of circulating glucocorticoid hormone and a reduced capacity for its binding, concomitant with some cognitive impairment (Angelucci et al., 1980; Sapolsky et al., 1983), heralded the "dust" stage. In addition, the atrophy of the hippocampus in Cushing's Disease (notwithstanding its reversibility and the fact that is accompanied by neither substantial cognitive disturbances, nor neuronal death), and the putative pathogenic role of hyperactive hypothalamo-pituitary-adrenal axis in major depression, also seen in some brain degenerative diseases, a neurotoxic action, particularly on the hippocampus, was somewhat hastily assigned to the glucocorticoid stress hormone by influential researchers (Landfield et al., 1978; Sapolsky et al., 1985). These workers were encouraged by the experimental demonstration that chronic exposure to stress or treatment with exogenous corticosterone could, via the local adrenocorticoid receptor, dam-

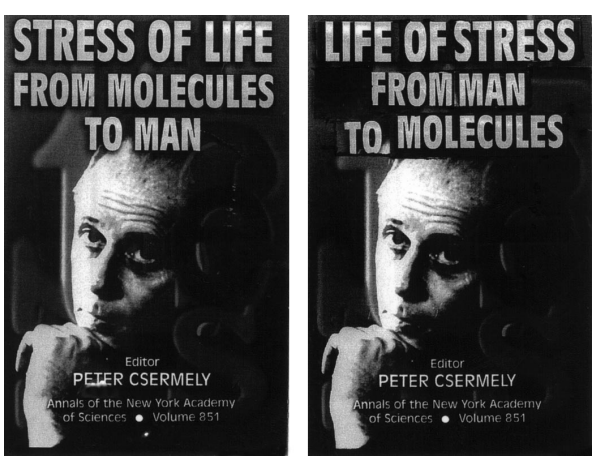


Fig. 3. Reversing the current popular image of stress to the idea of Hans Selye by reversing the sequence of the words in the title of a book.

Table 1
Spanish Great Inquisition models of "chronic" stress in the rat

Induction of chronic stress consisted of 20 days of the following stressors in a semi-random fashion	Stressed subjects received an array of stressors[a]
1–8 s 1 mA footshock for 60 min	sham adrenalectomy in ether anaesthesia
Food deprivation for 40 h	1 h mechanical shaking vibration
Cold swim at 7°C for 5 min	500 mU/kg lysine vasopressin s.c.
Water deprivation for 40 h	4°C cold environment exposure for 4 h
40°C heat exposure for 5 min	1 min ether exposure
200 rpm rotatory shaking for 30 min	1 mg histamine i.m.
Reversal of day/night cycle	Restraining in a tube for 1 h
Changing of cage mates	
on day 21, rats were exposed to bright light and 88 dB white sound for 1 h, then submitted to a 6-min behavioural test and collection of several arterial plasma samples during the subsequent 45 min	

[a] Stressors were applied three per day for 3 weeks and were rotated in sequence so as to avoid habituation.

age the morphology and function (cognitive and regulatory of the hypothalamo-pituitary-adrenal axis) of the hippocampus. This conclusion, postulating that life-long exposure of the hippocampus to the hormone can contribute to, or even induce an auto-reinforcing degenerative process typical of brain ageing, as well the concomitant cognitive disturbances and hyperactivity of the hypothalamo-pituitary-adrenal axis, became known as the "glucocorticoid cascade hypothesis" of Sapolsky et al. (1986). This hypothesis was widely accepted for many years in the neuroendocrine field. It now seems appropriate to reverse, as suggested by Fig. 3, the unnatural image of stress presented through the media and books popularising science. The true image, the scientific one, is that of a physiological concept of adaptation, and not that of a pathogenic mechanism. What follows is an attempt to restore glucocorticoid hormone to its place on the pedestal. To do this, one needs to re-examine the findings that had been seen as evidence of a neurotoxic action.

2. Experimental models of stress

For practical reasons, most of the experimental studies aimed at showing that exposure of humans to stress repeated throughout their life was a possible mechanism of brain ageing, or even of actual pathology, through the damaging action of the glucocorticoid "stress hormone", were done with rats. Extrapolation of findings from such studies is very limited, first because "repeated in the course of life" is not the equivalent of chronic daily exposure for 21 days — on average, one thirtieth of a rat's lifespan — to a set of ordeals, hopefully not to be encountered in the wild. Such were the models referred to in Table 1 under the heading inspired by a historical approach to torture. Extrapolation to the humans is further limited as the effect of such procedures results, not from stress as a physiological response, but from a global, severe disorder of a multiplicity of organs and functions.

3. Imitating stress with exogenous glucocorticoid hormone

Many studies infer that stress can be deleterious to learning and memory on the assumption that exogenous glucocorticoid hormone given to adrenalectomized or in-

Table 2
Neuroendocrine changes following different manipulations of the HPA axis

	Stress	Adrenalectomy	Exogenous glucocorticoid	"Anticortisols"	
				Glucocorticoid synthesis inhibition	Glucocorticoid receptor block
CRH	+	+	−	+	+
ACTH	+	+	−	+	+
LPH	+	+	−	+	+
β-Endorphin	+	+	−	+	+
Glucocorticoid	+	−	+	−	+
Glucocorticoid receptor	Activated	Inactivated	Activated	Inactivated	Inactivated
Negative feedback	On	Off	On	Off	Off
Immune activity:	Modulated	Unrestrained	Depressed	Unrestrained	Unrestrained if peripheral, depressed if central
(LPS-cytokine response, septic shock syndrome, autoimmune arthritis)					

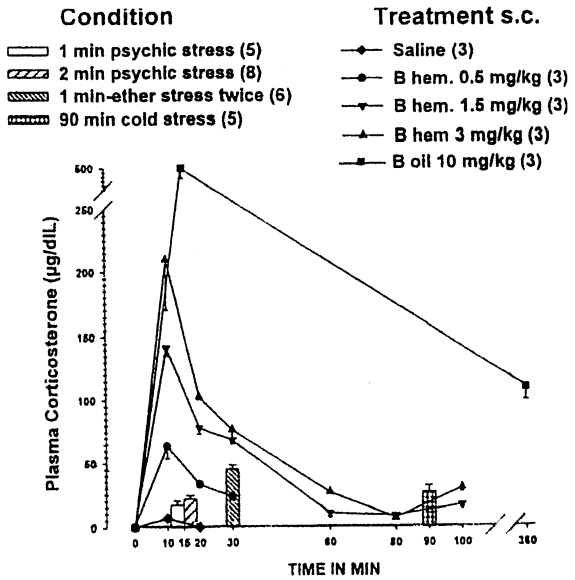


Fig. 4. The physiological or pharmaco-toxicological actions of the glucocorticoid hormone, endogenously released or exogenously derived, respectively, are determined by the plasma corticosterone concentrations reached in the rat following the exposure to stressors of different strength, or the administration at different doses.

tact animals, acutely and in minute doses, can imitate stress. Even if it were true that under these conditions the exogenous hormone can replace or reinforce, respectively, the action on end-targets of basal or stress-induced concentrations of the endogenous hormone, no imitation of stress is actually involved. Indeed, as illustrated in Table 2, a condition is produced which is precisely the opposite of, and seemingly counter to stress at all levels of the hypothalamo-pituitary-adrenal axis and of its whole suprahypothalamic afferent and efferent nervous regulation. The response to stress is much more than the mere increase in circulating glucocorticoid hormone.

Some researchers have assumed that predisposition to, or actual morphological and functional pathology of the hippocampus consequent to the continuous hypercorticism of "chronic stress" in the rat can be rather satisfactorily reproduced by the daily subcutaneous administration of the glucocorticoid for 3 weeks or 3 months, respectively. This procedure has no proper theoretical basis because the usual dose of 40 mg/kg, as initially suggested (Sapolsky et al., 1985), at each injection, as shown in Fig. 4, produces long-lasting high concentrations several orders of magnitude greater than the normal ones, even those seen after exposure to very intense stress. One should expect this dose to produce general cellular toxicity and thus no damage specific to the hippocampus. However, it is now clear that repeated stress exposure or chronic treatment with glucocorticoid does not as a rule lead to damage to the hippocampus. For instance, high doses of cortisol 4–6 mg kg^{-1} day^{-1} given for 12 months, while they obviously inhibit ACTH secretion do not affect hippocampal volume, total neuronal number or neuronal density in Macaca Nemestrina from 18 to 29 years of age. The authors of this report concluded that, unlike in rat, chronically elevated glucocorticoid concentrations, in the absence of stress, do not injure the hippocampus in old nonhuman primates (Leverenz et al., 1999).

4. Glucocorticoid hormone and neurogenesis

Very recently, results of years of work by Elizabeth Gould, Heather Cameron and Bruce McEwen on the suppression of cell division in the gyrus dentatus by the

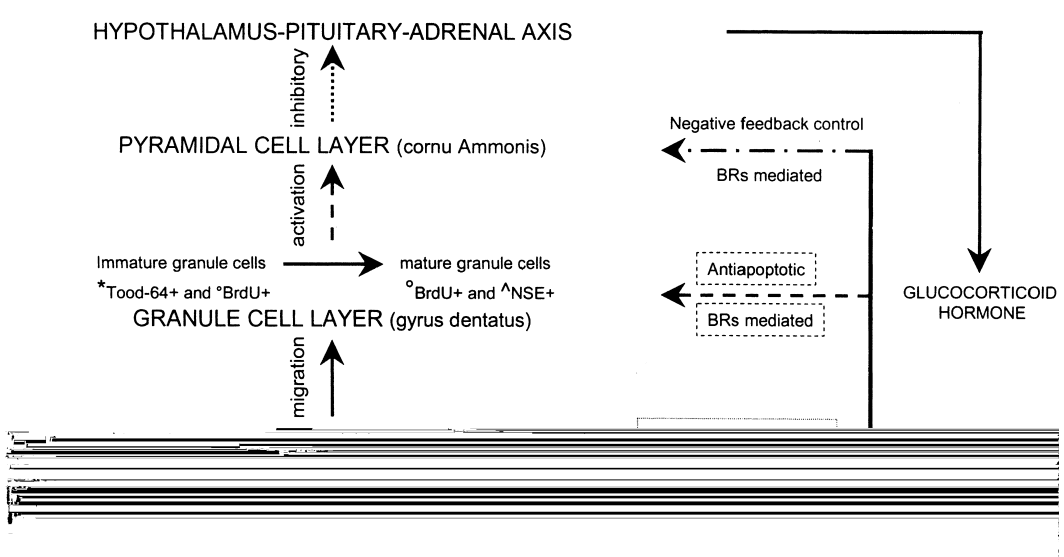


Fig. 5. The morpho-functional viability of the hippocampus in the course of ageing is governed by the local glucocorticoid hormone balancing action between neurogenesis and apoptosis in the dentate gyrus.

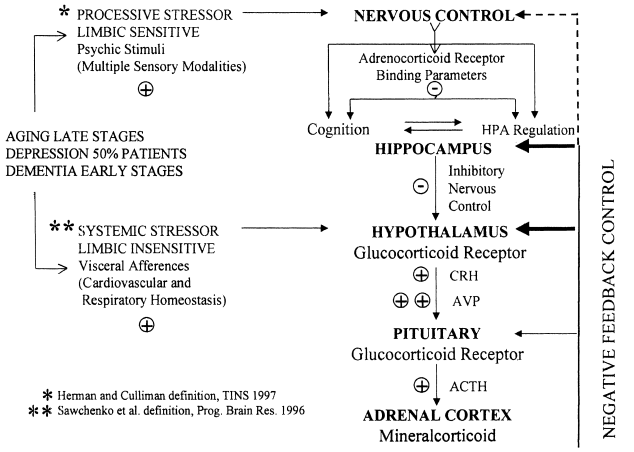
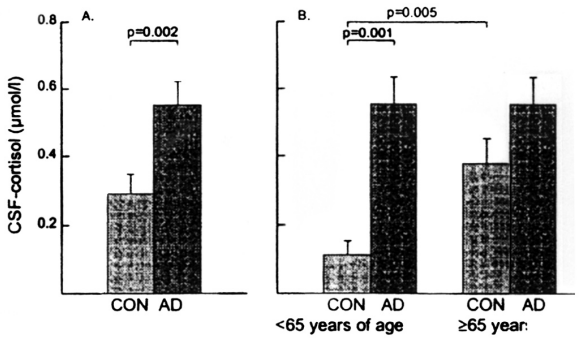


Fig. 6. Some degree of stress is continuously generated as an adaptive response in various conditions of suffering acting as stressors according to two different nervous modalities: processive or systemic.

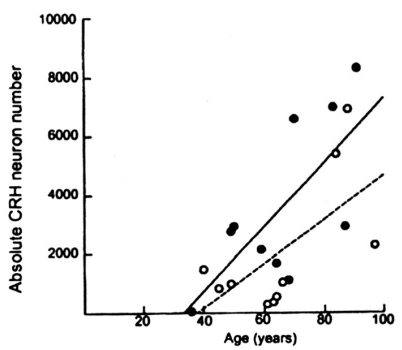
adrenal hormone, suggested a possible causative mechanism for the age-related memory deficits. The mechanism may involve an age-dependent block of neurogenesis in this important brain area by a marked age-dependent increase in corticosteroids levels, despite their significant role in the survival of mature granule cells. These deficits may be reversed by removal of corticosteroids (Cameron and McKay, 1999). The authors were surprised by the dramatic increase in the survival of young granule cells in the adult animal with hippocampus-dependent learning tasks, but not with random hippocampal activation or with learning tasks that do not require the hippocampus, disregarding the fact that the former tasks imply activation of the hypothalamo-pituitary-adrenal axis, namely a physiological degree of stress. However, as illustrated in Fig. 5, there could be a totally different interpretation for the role of the glucocorticoid hormone as affecting the cellular composition in the gyrus dentatus with progressive ageing. Instead of operating as a brake on the proliferation of precursor cells, thus impeding cellular renewal, the hormone could act as the "curator" of old granule cells which, with their long-acquired synaptic architecture, constitute a living museum of past experiences, the use of which is indispensable for survival. Further, the fact that the stress obviously associated with hippocampus-dependent learning tasks and involving transitory increases in glucocorticoid levels, favours the survival of newly formed granule cells (Cameron and Gould, 1994; Kempermann et al., 1998; Gould et al., 1999), is an indication of the positive role of the hormone as regards the formation of new memories. It is true that adrenalectomy acts as an accelerator for the production of new granule cells via proliferation of the precursors, but the necessarily associated pyknotic death of the mature granule cells now deprived from the hormone (Sloviter et al., 1989; Maehlen and Torvik, 1990) makes the animal blind, mute and deaf to any memories.

5. Glucocorticoid hormone, learning and memory

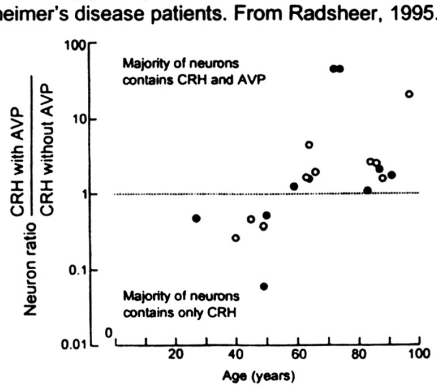
The mischief attributed in recent years to the glucocorticoid hormone also includes its ability to impair learning



Concentration of total cortisol in the ventricular cerebrospinalfluid in µmol/liter. A) Comparison of all controls with all Alzheimer patients. B) Comparison of controls with AD patients, and with old subjects after subdivision of the groups into subjects younger and older than 65 years of age.
From: Swaab et al., J. Neuroendocrinology, 1994.



Linear regression between age and absolute CRH cell number in the PVN. (•) and (—): control subjects; (o) and (- -): Alzheimer's disease patients. From Radsheer, 1995.



Age related increase in the ratios of the number of CRH neurons showing colocalization with AVP over those of CRH neurons not showing colocalization with AVP. Control subject (•), Alzheimer patients (o). From Radsheer, 1995.

Fig. 7. Changes in the activity of the pituitary–adrenal axis in the elderly and in Alzheimer's disease patients are accompanied by changes in the hypothalamic paraventricular nucleus (PVN) corticotropin-releasing hormone (CRH) cells.

and memory after modest, natural increases in its levels such as those occurring with ageing or stress. This is an extrapolation from experiments involving administration of high doses of glucocorticoid hormone to intact animals. In reality, the equivalent of maximum learning, in the form of hippocampal primed burst potentiation, is obtained in the adrenalectomized rat in the presence of blood concentrations of the hormone in the stress range, whereas above these levels learning is progressively impaired (Diamond et al., 1992). This is in full agreement with the two types of function, linear or U-inverted, expressing the relation between stress and learning, depending on task difficulty (and thus, it can now be added, on the plasma levels of the glucocorticoid hormone) according to the Yerkes–Dodson (1908) Law. Further, there is a facilitating effect of corticosterone on the hippocampus-dependent spatial memory formation in the water maze, measured as the degree of retrieval performance, provided that the action is experience-dependent with regard to stimulus intensity. Less stressful training is accompanied by a lower increase in plasma corticosterone levels and produces a lower degree of learning than does a stronger stress (Sandi et al., 1997).

With regard to memory, an impairing action of stress or exogenous glucocorticoid hormone has been assumed on the basis of experimental findings that disregard physiological regulation of the hippocampus/hypothalamo-pituitary-adrenal axis system. For instance, it has been shown that exposure to footshock 30 min before, but not 2 min or 4 h before a retention test in a water-maze spatial task, impairs the retrieval of long-term spatial memory in the rat. Because the same effect is obtained by giving corticosterone (at the not inconsiderable dose of 3 mg/kg s.c.) to nonstressed rats, it is concluded that circulating glucocorticoid hormone is to blame for the memory defect (de Quervain et al., 1998). The authors do not consider what is the most likely mechanism of the defect, namely that, at the time of retention testing, the animal is at the apex of a transitory block, via the negative feedback exerted by the previous increase in circulating hormone, of the hypothalamo-pituitary-adrenal axis, the activation of which is required for the behavioural performance. The finding that, in humans, administration of cortisone, 25 mg, 1 h before a delayed free-recall test impairs retrieval of long-term declarative memory (de Quervain et al., 2000) is interpreted the same way.

6. Glucocorticoid increase in ageing and brain degenerative processes

A progressive increase in levels of circulating cortisol occurs with increasing age, as well as in brain degenerative processes, for instance in Alzheimer's disease and multiple sclerosis. This has been interpreted as a malfunction of the hypothalamo-pituitary-adrenal axis, and, according to the glucocorticoid-cascade hypothesis, is considered as a main agent of injury to the hippocampus and to lead to the cognitive impairment of the elderly, and as an added pathogenic factor in brain degeneration. However, as illustrated in Fig. 6, some degree of stress is present under condition involving bodily or psychic suffering depending on the two different ways the stressor activates the hypothalamo-pituitary-adrenal axis. Under such conditions the homeostatic adjustment is carried out successfully or at least attempted, with an adequate change in the nervous regulation of the sensitivity of the glucocorticoid receptors in brain to negative feedback in response to the circulating hormone (Casolini et al., 1993; Alemà et al., 1995), and consequently an adequate change in the cognitive and neuroendocrine–hormonal regulatory activity of these re-

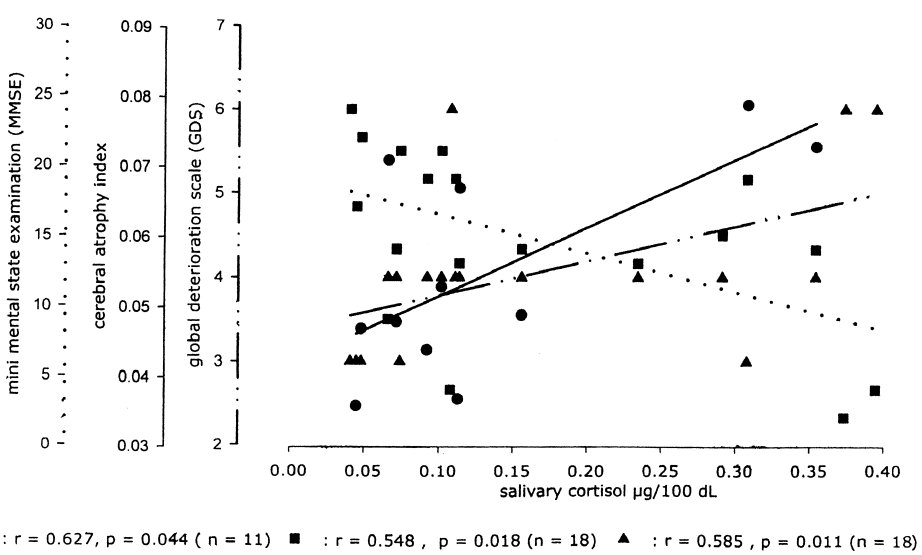


Fig. 8. Analysis of the correlations between salivary cortisol and clinical parameters, cognitive, behavioural and morphological in Alzheimer's disease patients.

ceptors. This consideration introduces the only seemingly paradoxical concept of physiological usefulness of the hypercortisolemia — in the range of modest stress levels — seen (Fig. 7) in many elderly people and in Alzheimer's patients (Swaab et al., 1994). It results not from a disinhibited adrenal secretion, but, as illustrated in the same figure, from an increased neuroendocrine-competent cellular substrate in the hypothalamus (Raadsheer et al., 1995). Indeed, this phenomenon could be adaptive in nature, aimed to antagonise the inflammatory component of the variously advanced degenerative processes in the ageing brain, the frankly demented brain and in multiple sclerosis. It is a serious handicap that the hypercortisolemia in this disease, so strongly characterized by acute inflammatory activity in the central nervous system, has been considered simply expressive of a mood disorder (Fassbender et al., 1998).

In a study on Alzheimer's patients, we found their cortisol secretion circadian rhythm to be set higher than that of age-matched controls, and, as illustrated in Fig. 8, that the degree of their hypercortisolemia is strongly positively correlated with the extent of mental and behavioural deterioration, and strongly negatively correlated with the degree of cerebral atrophy (Angelucci et al., 2000). Far from ascribing these correlations to a pathogenic role of hormone increase, we interpret them, as sketched in Fig. 9, as the indication of a progressive stress adaptive response aimed at opposing cortisol, the endogenous anti-inflammatory to cytokine and prostaglandin, the endogenous pro-inflammatories. In order to support this hypothesis, we have devised a study aimed at ascertaining whether contrasting the age-dependent increase in the rat brain concentration of cytokine and prostaglandin, an event analogous to that in brain degenerative processes in humans, concomitantly prevents the age-dependent increase in circulating glucocorticoid hormone. Rats were treated with the cycloxygenase 2 selective inhibitor, celecoxib, 3 mg/kg os twice a day for 4 months starting at age 12 or 18 months. We

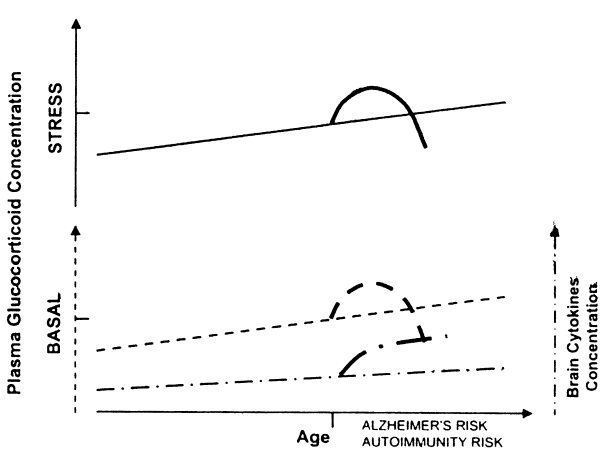
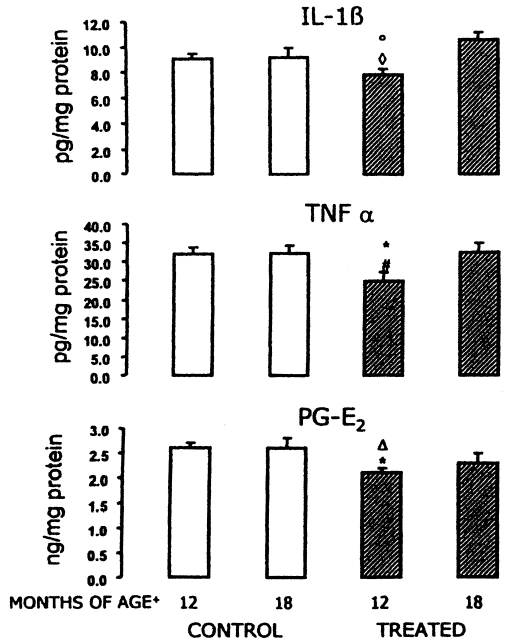


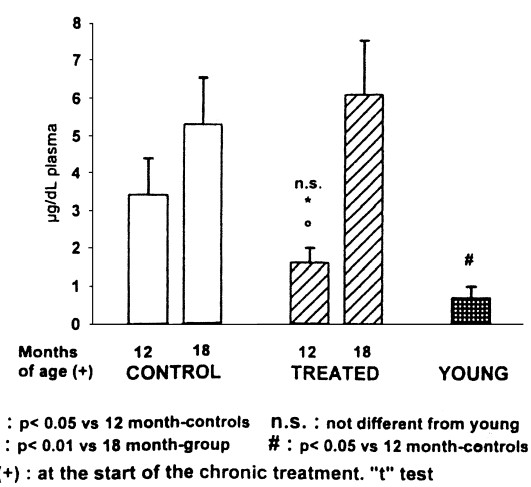
Fig. 9. Changes in basal and stress activity of the hypothalamo-pituitary-adrenocortical axis and in brain concentration of pro-inflammatory–immunogenic cytokines in ageing normal humans and in Alzheimer's disease patients (tick segment).



IL-1ß and TNFα assayed with ELISA, PG-E_2 with EIA. +: at the start of the chronic treatment; °: p<0.05 v. 12 month-control; *: p<0.01 v. 12 month-control; #: p<0.01 v. 18 month-treated; ◊: p<0.05 v. 18 month-treated; Δ: p<0.05 v. 18 month-control. n=8 per group with t-test.

Fig. 10. Concentrations of interleukin-1β (IL-1β), tumour necrosis factor α (TNF-α) and prostaglandin E_2 (PG-E_2) in the hippocampus after 4 months of treatment with celecoxib 3 mg/kg os twice in day in singly caged male Wistar rats of different ages.

measured the concentration of inflammatory cytokines and prostaglandin in the hippocampus, an "Alzheimerian" region, the plasma concentration of corticosterone, and the rats' cognitive and emotional performance. The treatment successfully reduced the increase of interleukin-1β, tumour necrosis factor-α and prostaglandin E_2, as illustrated in Fig. 10, and maintained plasma corticosterone, as illustrated in Fig. 11, as well as spatial learning, as illustrated



°: p< 0.05 vs 12 month-controls n.s.: not different from young
*: p< 0.01 vs 18 month-group #: p< 0.05 vs 12 month-controls
(+): at the start of the chronic treatment. "t" test

Fig. 11. Plasma corticosterone concentrations after 4 months of treatment with celecoxib 3 mg/kg os twice in day in singly caged Wistar rats of different ages.

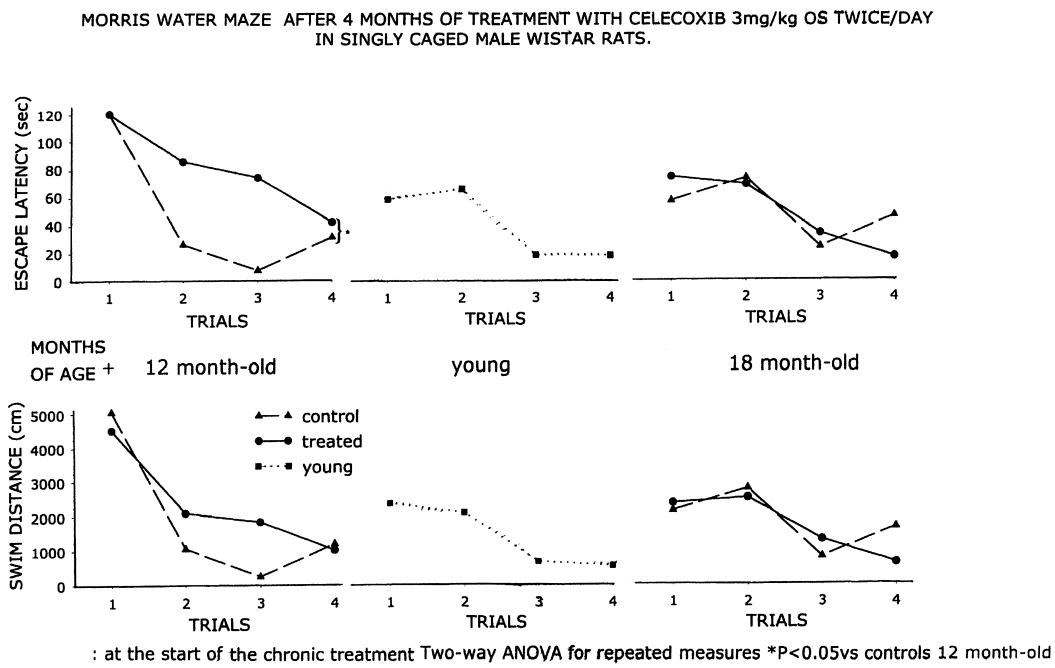


Fig. 12. Learning performance in the Morris water maze after 4 months of treatment with celecoxib 3 mg/kg os twice in day in singly caged Wistar rats of different ages.

in Fig. 12, at levels similar to those in young rats (3 months of age).

If the view we derive from our studies truly reflects the meaning of the increase in the activity of the hippocampus/hypothalamo-pituitary-adrenal axis in Alzheimer's disease, the use of glucocorticoids might still be advisable, provided that cortisol is used. The paradox of adding cortisol to cortisol may be more apparent than real: synthetic glucocorticoids bind poorly to transcortin, apart from prednisolone, and are incompatible with the circadian rhythm of hormonal glucocorticoid activity, due to their long plasma and biological half-life. More importantly, synthetic glucocorticoids block the production of the adrenal hormone from which, due to the presence in their molecule of a supplementary double bond, they differ substantially; the difference particularly affects their binding capacity to the two types of adrenocorticoid receptors in the brain. Consequently, they lack the ability to preserve the granule cells of the dentate gyrus, while endangering them in a way that would be antagonised by the natural hormone (Hassan et al., 1996).

In the end, in spite of the totally negative results of the study of 1-year prednisone treatment in Alzheimer's disease, which also showed that prednisone led to a greater decline in memory with a trend to a greater decline in orientation (Aisen et al., 2000), the therapeutic use of anti-inflammatory steroids in this disease still remains open to evaluation.

It is fitting to conclude with the mentioning of two Jubilees in the Year 2000: that of the Nobel Prize for the discovery of the glucocorticoid hormone, and that of David De Wied's 75th birthday, and lastly a thought for the pioneer, Hans Selye.

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