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## Hippocampal damage mediated by corticosteroids – a neuropsychiatric research challenge

**Abstract** There is an increasing evidence that corticosteroids damage the hippocampus in rodents and in primates. Hippocampal atrophy induced by corticosteroids may play an important role in the pathogenesis of a range of neuropsychiatric disorders. Hippocampus is necessary for short-term memory consolidation and HPA axis regulation. Signs of hippocampal damage (HPA dysregulation in combination with memory impairment) are found in affective disorders, Alzheimer's disease and in posttraumatic stress disorder. MRI volumetry reveals reduced hippocampal volume in these diseases. Evidence supporting the "glucocorticoid hypothesis" of psychiatric disorders is reviewed in the first part of the paper. Unresolved questions concerning temporary aspects of neurodegeneration, causality, reversibility, type of damage, factors increasing hippocampal vulnerability, and both pharmacological (CRH antagonists, antiglucocorticoid drugs, GABA-ergic, serotonergic, glutamatergic agents) and non-pharmacological (psychotherapy) treatment approaches are discussed in the second part.

**Key words** Hippocampus · corticosteroids · affective disorders · posttraumatic stress disorder · Alzheimer's disease

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### Hippocampus and HPA activity

Variations in neurotransmitters and their receptors no longer seem to be the only satisfactory models to explain

neurobiological basis of psychopathology. To study neurodegenerative effects of corticosteroids, particularly on the hippocampus represents a promising novel approach to (and insight into) the aetiology and pathogenesis of various neuropsychiatric disorders.

Hippocampus is the prominent target structure for the activity of corticosteroids in the brain. In animals, corticosteroid hormones have been shown to diminish the number of branch points and length of dendrites in hippocampus of rats (Watanabe et al. 1992a, Magarinos and McEwen 1995a), to cause dendritic atrophy of pyramidal neurons in the hippocampus (Watanabe et al. 1992b), and even lead to loss of CA3 and CA4 hippocampal neurons (Mizoguchi et al. 1992). High levels of adrenal steroids facilitate the hippocampal damage following neurotoxin infusion (Sapolsky 1985a) and ischaemia in rats (Sapolsky and Pulsinelli 1985). Similar results have been obtained in primates (Sapolsky et al. 1990).

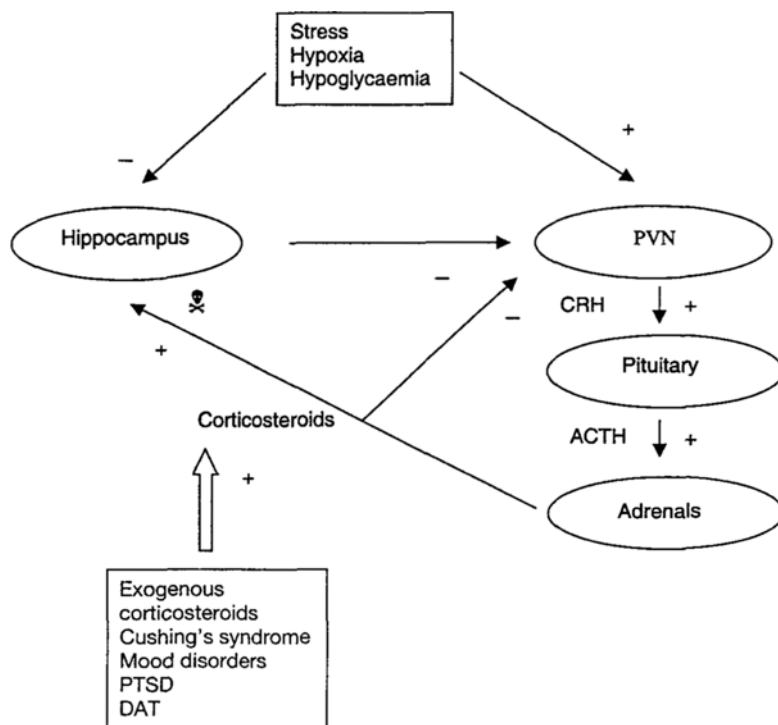
The hippocampus plays an important role in the negative feedback control of the hypothalamo-pituitary-adrenal (HPA) axis response to stress (Fig. 1). As plasma corticosteroid concentrations rise during stress, glucocorticoid receptors abundant in the hippocampus are activated in order to mediate the fast feedback inhibition of HPA axis. Excision or impairment of the hippocampus significantly reduces the inhibitory effects of dexamethasone on the stress-induced adrenocortical response (for review see (Checkley 1996) (Feldman and Weidenfeld 1995). Abnormal activation of HPA axis is a common hallmark of various neuropsychiatric disorders. Non-suppression of cortisol in the dexamethasone suppression test (DST) is an important sign of HPA hyperactivity and is frequently present in depressed patients. Analysis of 150 studies showed that overall sensitivity of DST in major depressive disorder ( $n = 5111$  cases) reaches 44.1% and even 67% in patients ( $n = 150$ ) with psychotic depression (Arana et al. 1985).

Also among patients with Alzheimer's dementia (DAT), significantly more DST non-suppressors are found compared to healthy subjects. This may be partly explained by comorbidity with depression. However,

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**Fig. 1** Vicious circle of hippocampal neurodegeneration mediated by corticosteroids. HPA activation in healthy subjects is under the negative feedback of corticosteroids, which turns the HPA axis off directly in hypothalamus and indirectly via the hippocampus. Excessive exposure to corticosteroids and other factors can lead to the damage of the hippocampus and impairment of its inhibitory effect on the hypothalamus. This results in HPA hyperactivity, hypercortisolemia and further hippocampal damage.



DST non-suppression has been described also in non-depressed DAT patients (Greenwald et al. 1986).

Acute or chronic stress is another condition associated with major release of corticosteroids (Kirschbaum et al. 1996). In this respect, the findings of lower mean 24-hour urinary cortisol (UFC) excretion and enhanced cortisol suppression after low-dose of dexamethasone in posttraumatic stress disorder (PTSD) are interesting and somewhat paradoxical (Yehuda et al. 1995, Stein et al. 1997a).

### Hippocampus and memory

The hippocampus is involved in short-term memory consolidation (Giap et al. 2000). Short-term declarative memory deficits were reported in subjects exposed to high levels of exogenous corticosteroids (Wolkowitz et al. 1990, Newcomer et al. 1994) as well as of endogenous corticosteroids due to Cushing's disease (Starkman et al. 1992, Mauri et al. 1993, Bender et al. 1991). They are also common in depression (Wolkowitz et al. 1990, Sheline et al. 1999), PTSD (Bremner et al. 1993), stress (Kirschbaum et al. 1996), and of course in DAT. In depression, the severity of cognitive impairment correlated positively with mean UFC levels (Rubinow et al. 1984), and in bipolar patients with total lifetime duration of manic and depressive episodes (van Gorp et al. 1998). These data suggest the potential relevance of corticosteroids for hippocampus-mediated declarative memory damage in humans.

Changes in HPA axis activity, hypercortisolemia and memory impairment are the common symptomatic cluster present in various neuropsychiatric disorders. They point towards the importance of the hippocampus in the aetiopathogenesis of these disorders. Are there any morphological findings supporting this hypothesis?

### Structural changes of the hippocampus in man

In 3 of 12 patients suffering from Cushing's syndrome (9 patients with ACTH dependent CS, 2 with ACTH independent CS, one with rare syndrome of intermittent hypercortisolemia and partial cortisol receptor insensitivity, rough duration of the disorder 1–4 years), the hippocampal volume expressed as a percentage of total intracranial volume was below the 95% confidence interval for population norms. More severe atrophy was associated with more pronounced hypercortisolism (Starkman et al. 1992). In the second study, 17 months (range 5–52) after the surgical treatment and decrease of cortisol levels in patients with ACTH dependent CS, significant hippocampal volume enlargement was observed (Starkman et al. 1999).

Several studies noted hippocampal atrophy in various psychiatric disorders as mentioned above. Ten women with a history of prolonged, severe depression, in remission from 6 months to 4 decades at the time of the study had significantly reduced bilateral hippocampal volume (15% and 11% for the left and right hippocampus respectively) in comparison to matched control

subjects (Sheline et al. 1996). Also in 24 women with the history of severe depression and currently in remission for a minimum of 4 months, the hippocampal volume was significantly decreased compared to matched controls. The reduction in left and right hippocampal volume reached 10% and 8% respectively. There was a significant negative correlation between hippocampal volume and total lifetime duration of the illness (Sheline et al. 1999). A third report concerned 16 patients with major depression in remission (average of 7 months) and 16 case-matched non-depressed control subjects. Patients with the history of depression had significantly smaller left hippocampal volume (by 19%) than control subjects. This reduction was not accompanied by smaller volumes of the amygdala, caudate, frontal lobe, temporal lobe or the whole brain (Bremner et al. 2000).

A number of studies (Swayze et al. 1992, Dupont et al. 1995) failed to observe any changes of hippocampal volume in patients with severe depression. However, these studies used mostly older and less sensitive MRI technology. The controversy could be speculatively explained also by a methodological bias of "positive" studies, in which the smaller hippocampal volume is caused either by the loss of water (see the discussion below – *The character of changes mediated by corticosteroids*) or by non-specific glial changes. Interesting are the findings in PTSD. Twenty-six Vietnam combat veterans had a significant 8% decrease of the right hippocampal volume and non-significant 3.8% decrease of the left hippocampal volume and short-term memory deficit compared to healthy subjects matched by age, sex, race, education, body size, socio-economic status, and years of alcohol abuse (Bremner et al. 1995). A comparison of 7 Vietnam veterans suffering from PTDS with 7 veterans without PTDS and 8 healthy non-veterans showed significant bilateral hippocampal atrophy (26% and 22% in the left and right hippocampus respectively) in PTDS patients. The two other groups did not differ significantly (Gurvits et al. 1996).

Two studies on PTDS arising from child sexual or physical abuse also confirmed the hippocampal atrophy (Bremner et al. 1997, Stein et al. 1997b).

Decreased hippocampal volume is one of the first signs of DAT and is one of the risk factors for the development of this type of dementia (Convit et al. 1997).

There is a large overlap between symptoms of Cushing's disease, affective disorders, PTDS and DAT. One of common signs of these disorders is hypersecretion of corticosteroids and hippocampal atrophy. The corticosteroid hypothesis of psychiatric disorders gives rise to a wide range of questions. Some of them are discussed below.

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### Temporal aspects of neurodegeneration after corticosteroids

What is the duration of exposure to corticosteroids necessary for the morphological changes to occur? Hip-

poampal atrophy in rats appeared only after 3 weeks of intense stress, while 2 weeks were not enough (Magarinos and McEwen 1995a). In primates (4 vervet monkeys) marked neuropathological changes in CA2 and CA3 cell fields were seen one year after the implantation of cortisol pellets into their hippocampi (Sapolsky et al. 1990). The goal of this study, however, was not to assess the temporal aspects of neurodegeneration, so changes might have occurred in fact earlier.

In men, cognitive impairment is evident already after a single dose of 1 mg of dexamethasone or 10 mg of cortisol (Wolkowitz et al. 1990, Kirschbaum et al. 1996). This effect is definitely not due to neurodegeneration but seems to be mediated by the agonistic action of corticosteroids and its metabolites on GABA<sub>A</sub> receptors (Puia et al. 1990).

It is currently almost impossible to estimate the critical duration of corticosteroid hyper-exposure necessary for the structural changes in the hippocampus to occur. A prospective study in patients treated with high doses of corticosteroids might give an answer. In our current study we chose patients suffering from Pemphigus vulgaris and Bulous pemphigoid as a model of exposure to high doses of corticosteroids. The advantage of studying just these disorders is that they primarily affect the skin and mucous membranes, but not the brain. Their direct or indirect effects on the brain would confound studies of other more common conditions treated by corticosteroids, such as rheumatic diseases, anaemia or bronchial asthma. The results should be always carefully adjusted to the age, as higher age is significantly related to both changes in HPA axis regulation and brain atrophy.

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### The reversibility of damage induced by corticosteroids

Is the neurodegeneration mediated by corticosteroids reversible? Hippocampal volume reduction is visible in patients with the history of affective disorders still years after the last depressive episode and even in subjects with restored or normal cortisol levels. These findings suggest at least partial irreversibility of corticosteroid-induced neurodegeneration. It would be interesting to determine whether non-suppression in DST correlates with the total number of depressive episodes in the patients' history and whether DST non-suppressors differ from suppressors in terms of memory or cognitive impairment. A retrospective study addressing this issue shows that non-suppressors had longer duration of the disease and longer cumulative duration of past affective episodes (Lenox et al. 1985). It is impossible, however, to decide whether a more chronic disorder leads to the non-suppression or vice versa. The large comparative analysis shows that the sensitivity of DST among elderly patients (over 60 years) with depressive illness is 1.5 to 1.9 times higher than in the total group of adult patients, indicat-

ing increased rate of non-suppression in elderly depressed patients (Arana et al. 1985). This can be either due to the association of non-suppression with age or with the longer duration of the disease.

Changes in human hippocampal formation volume (HFV) associated with sustained hypercortisolemia seem to be reversible, at least in part, once cortisol levels decrease. Following the treatment of patients with Cushing's syndrome, HFV increased by up to 10% (average from 2620 mm<sup>3</sup> to 2700 mm<sup>3</sup>). Increase in HFV was significantly associated with magnitude of decrease in UFC (Starkman et al. 1999). Further argument for the possible reversibility of neurodegenerative changes is the fact that neurogenesis occurs to some extent even in adults (Gould and Tanapat 1999). So loss of neurons is not inevitably irreversible. The question remains whether hippocampal volume can be restored to its original extent.

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### Are corticosteroids really the damaging agent?

Depression is associated with several potentially neurotoxic factors (elevated levels of CRH in CSF, increased number of CRH secreting neurons in limbic regions, increased numbers of vasopressin-expressing neurons in the paraventricular nucleus-PVN, etc. – for review see Holsboer 2000). There is no study showing clearly that the hippocampal atrophy in depressive patients is associated exclusively with hypercortisolaemia. About half of depressed patients are DST non-suppressors. If corticosteroids were the damaging agent, then the proportion of depressed patients with diminished hippocampal volume should be approximately 50%. This is not the case. The higher proportion of patients with hippocampal atrophy can be speculatively explained by the possibility that DST non-suppression and/or elevated cortisol levels occurred sometimes in the history of patients, in which the atrophy is not associated with current DST non-suppression. Moreover, a single DST result does not reflect long-term corticoid status (for review see Sapolsky 2000).

Controversial are also the findings of lower hippocampal volume in PTSD, which is not usually associated with hypercortisolaemia. It is possible that excessive hypercortisolaemia in the time of trauma may have damaged the hippocampus. One can speculate that increased sensitivity of glucocorticoid receptors in PTSD could be the common denominator of both lower plasma cortisol caused by enhanced HPA sensitivity to feedback (Yehuda 2001) and the neurodegenerative effects of corticosteroids.

Evidence supporting the role of corticosteroids in neurodegenerative changes is still growing and involves the anatomical and neuropsychological findings in Cushing's syndrome, frequent occurrence of memory deficits in patients treated with corticosteroids and the improve-

ment of these changes following the normalisation of cortisol levels. In animals, the neurodegenerative effects of corticosteroids have been rather clearly demonstrated.

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### Causality

The causality of the above listed changes still remains to be a crucial problem. What was first, the disease symptoms or diminished hippocampus? Is the hippocampal atrophy the cause or the consequence or is it rather parallel to above-mentioned disorders? For example, in Vietnam veterans, primarily smaller hippocampal volume might lead to insufficient cognitive strategies predisposing them rather to combat exposure than to safer work in the office. A small hippocampus may also lead to depressogenic cognitive strategies (learned helplessness, decreased ability to choose the correct coping strategy). It is difficult, however, to think of a way in which decreased hippocampal volume could cause peripheral Cushing's syndrome (the central one can be explained by the impaired negative feedback mediated by hippocampus) or sexual abuse in childhood (physical abuse could be elicited by impaired cognitive functions). Moreover, in depressed patients hippocampal atrophy was a function of the illness duration and not of the severity of depression. Also development of clinical symptoms and/or neuroendocrine imbalance seem to precede the decreased hippocampal volume (Bremner et al. 2000; Sapolsky 2000). Finally, in one prospective study, MRI was carried out almost immediately at the time of a trauma (in most cases, a serious car accident) and at various intervals thereafter. Among those who developed PTSD (N = 10), hippocampal atrophy could not be demonstrated even 6 months after the trauma, which again argues against the hypothesis of hippocampal damage preceding the disorder (Shalev et al. 1999).

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### The character of changes mediated by corticosteroids

Do corticosteroids cause cell death and neuronal loss or do they cause atrophy or degeneration? This question has not been clearly addressed even in animal models. The majority of animal studies report only atrophy of dendritic branches. This can be the first step in the process leading to necrosis and neuronal loss. However, neuronal cell death was found only in a few studies.

The interpretation of human data is even more complicated. MRI revealed that hippocampal atrophy could be caused by the decrease in dendritic branching or by loss of water and not by neuronal loss. Loss of water does not seem to explain changes, which are rather selective to the hippocampus and usually do not affect the whole brain volume. On the contrary, antioedematous effects of corticosteroids are diffuse and should be therefore found

in the whole brain. Water loss also does not explain the long-lasting hippocampal and memory changes observed even in patients with normal cortisol plasma levels. Post-mortem studies as well as *in vivo* measures of N-acetyl aspartate (NAA, a marker of neuronal density) using MR spectroscopy could help to clarify this question. There is a single unpublished work mentioned in review by Brown et al. (1999), reporting the reduction of the NAA signal from the hippocampus in patients with Cushing's syndrome. Normalisation of cortisol levels led to an increase in NAA concentration.

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### Increased HPA sensitivity to stress

What is the mechanism of the increased HPA sensitivity to stress? Animal studies show that early traumatic experience can change the sensitivity of the HPA axis by altering the expression of relevant genes, e.g., for CRH, CRH receptors, glucocorticoid receptors (GR), and central benzodiazepine receptors (BDR).

Maternal care is paramount for the long-term adjustment of HPA axis reactivity in the offspring of rodents and primates. Handling of rat pups, i.e. short-term (15 minutes) isolation of pups from their mothers, repeated daily for 2–3 weeks, increases the maternal care assessed as the frequency of licking-grooming and arched back nursing behaviour. Handled pups had increased levels of mRNA for GR II in hippocampus, decreased levels of mRNA for CRH in PVN, increased levels of BDR in amygdala in comparison with non-handled pups. Handled pups were less fearful, had better spatial memory and higher density of CA1 and CA3 neurons in the hippocampus. Variations in maternal care caused by environmental changes (handling of pups) change the expression of genes important for neuroendocrine and behavioural reactions to stress. These changes persisted throughout the lifetime (Meaney et al. 1991).

Similar mechanisms seem to be active in humans. Early traumatic experience has long-term effects on psychological development. Childhood sexual abuse is associated with higher incidence of depression in adulthood. Patients with mood disorders have more often a history of sexual abuse in childhood (Weiss et al. 1999). Parental divorce or loss of a parent, death of a sibling, and physical or sexual abuse in childhood are often present in the history of patients with agoraphobia or panic disorder (Shear 1996) and in adult suicide attempters (de Wilde et al. 1992). These conditions seem to be related to persisting dysregulation of the HPA axis. Thirteen sexually abused girls, currently without symptoms of depression, 1–12 years after the abuse still showed significantly lower basal and oCRH-stimulated ACTH levels compared to control subjects. Their total basal, free basal and oCRH-stimulated plasma cortisol levels as well as 24-h UFC measures, however, were similar to those in controls (De Bellis et al. 1994). Such findings are typical for depressed patients and can be interpreted as decreased

sensitivity of the pituitary gland to CRH and increased sensitivity of adrenals to ACTH, possibly due to chronic or intermittent hypersecretion of CRH during the traumatic experience. There is also other evidence for the key role of HPA axis dysregulation in long-term vulnerability to stress. Both depressed and non-depressed women with the history of abuse had higher ACTH levels during psychosocial stress, than non-abused women. Depressed abused women exhibited more than 6-fold greater ACTH response to stress than age matched controls (Heim et al. 2000).

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### Therapeutical possibilities

There are many therapeutic approaches targeting the activity of the HPA axis. These drugs can act at several levels – CRH or GR, synthesis and release of corticosteroids, or other systems participating in changes mediated by adrenal steroids.

So far two types of receptors for CRH – CRH1 and CRH2 – have been described. CRH1 receptor probably mediates anxiogenic properties of CRH (Smagin and Dunn 2000). The CRH1 antagonist R121919 seems to be safe and well tolerated in man. Dose dependent significant reductions in depression and anxiety scores using both patient and clinician ratings were observed during the treatment with this compound in an open study. Discontinuation of treatment led to worsening of affective symptomatology. However, more data in double-blind placebo controlled studies are needed to confirm the therapeutic potential of this compound. It is interesting that CRH1 receptor blockade did not impair the ACTH and cortisol secretory activity either at baseline or following an exogenous CRH challenge. The doses used either did not lead to the complete suppression of CRH1 or CRH2 receptors compensated for this blockade (Zobel et al. 2000). An important question is, what would happen after a rapid R121919 withdrawal. Receptor blockade usually leads to its up-regulation and accumulation of specific ligands (agonists). After rapid treatment cessation, an increased CRHR expression combined with accumulation of CRH could have dangerous consequences.

There is some evidence of antidepressant effects of antiglucocorticoid drugs. Six out of eight patients suffering from treatment-resistant depression responded to a 2-month treatment with antiglucocorticoid drugs (aminoglutethimid, ketoconazol, metyrapone) without concomitant antidepressant therapy (Murphy et al. 1991). However, lack of control groups makes it impossible to come to any conclusions. Other open label studies on the same topic confirm the previous findings (for review, see Murphy 1997). There are two double-blind placebo controlled studies evaluating the therapeutical efficacy of ketoconazole in depression. In the first one, none of the 8 patients given placebo improved, whereas 2 of 8 treated with ketoconazole met criteria for a posi-

tive response. Nevertheless, mean changes in HAM-D scores did not differ significantly between groups (Malison et al. 1999). In the second study, ketoconazole compared to placebo was associated with improvements in depression ratings in the hypercortisolaemic, but not in the non-hypercortisolaemic patients (Wolkowitz et al. 1999). The efficacy of antigluco-corticoid drugs in the treatment of depression cannot be explained simply by the decrease of cortisol levels, because this should induce the release of CRH leading to the worsening of depression and anxiety. Antigluco-corticoid drugs also inhibit enzymes necessary for cortisol synthesis. Such an inhibition leads to accumulation of metabolites (C11 non-hydroxylated steroids, alopregnanolon), which are psychoactive and may suppress CRH release, thus compensating for the lack of cortisol (Holsboer 2000).

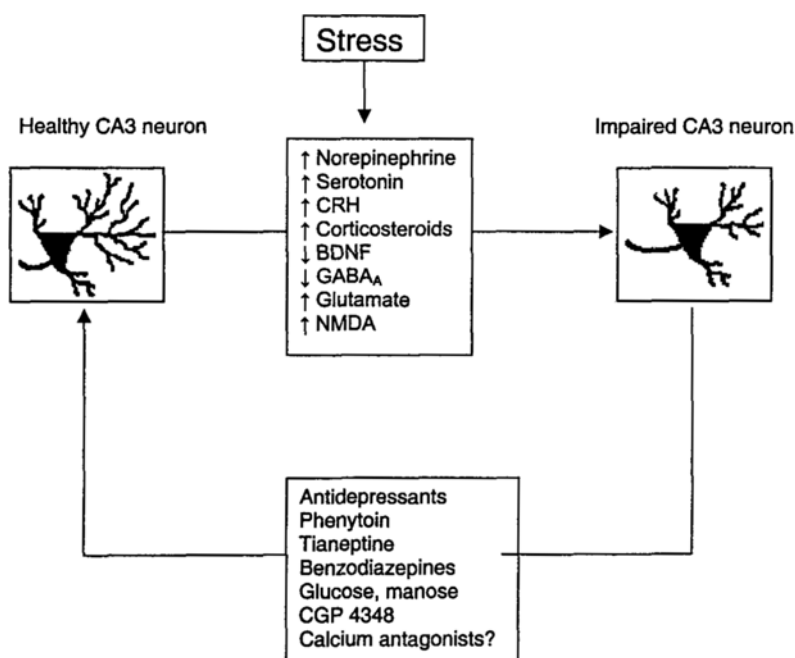
Corticosteroids also affect various neurotransmitter systems. They potentiate the release and inhibit the reuptake of glutamate, increase the expression of NMDA receptors (for review see McEwen and Magarinos 1997), increase the vulnerability of neurons to metabolic insults and hypoxia (Sapolsky 1985b, Sapolsky and Pulsinelli 1985), decrease the expression of neurotrophic factors (BDNF) (Smith et al. 1995), and decrease the activity of GABAergic inhibition (for review see McEwen et al. 1997). Glutamate mediated NMDA receptors activation, without proper GABA inhibition, and potentiated by serotonin leads to influx of calcium into cells. High intracellular calcium concentrations cause depolymerisation of cytoskeleton, autolysis and even neuronal death (excitotoxicity). Antagonists of NMDA receptors (CGP 4348), antagonists of excitatory amino acids (Phenytoin) (Magarinos and McEwen 1995b, Watanabe et al. 1992b),

GABA agonists (Magarinos et al. 1999), serotonin reuptake enhancers (tianeptine) (Watanabe et al. 1992c), energetic substrates (glucose, manose) (Sapolsky 1986) or antidepressants which activate the pathway leading to synthesis of CREB and subsequently to BDNF expression (Nibuya et al. 1996), all exert neuroprotective effects in animal studies (Fig. 2). It is surprising that nobody has so far systematically tested neuroprotective effects of calcium channel blockers (CCBs) or peroral antidiabetics in similar settings. In affective disorders, CCBs play so far only very limited role (rev. Höschl 1991).

### Non-pharmacological modification of HPA axis activity

Is it possible to tune the activity of the HPA axis by non-pharmacological means? Following 12 cognitive-behavioural therapy (CBT) sessions lasting 30-60 minutes, 19 out of 29 unmedicated depressed inpatients (with the mean HAM-D score prior to treatment 21.8) showed more than 50% reduction in the HAM-D or the final score was less than 10. Non-responders in comparison to responders had significantly increased pre-treatment UFC levels and were more often DST non-suppressors (Thase et al. 1996). Due to the absence of control group and post-treatment measurements of cortisol levels, it is impossible to come to any conclusion about the effects of psychotherapy on the activity of HPA axis. Further studies are needed to elucidate the therapeutic potential of psychotherapy in reversing the HPA hyperactivity.

**Fig. 2** Hippocampal CA3 pyramidal cells neurodegeneration mediated by corticosteroids and its pharmacological treatment. Stress activates norepinephrine and serotonin systems, leading to the release of CRH, ACTH and corticosteroids. Corticosteroids facilitate glutamatergic neurotransmission and decrease the GABAergic tonus, resulting in neuronal damage. Corticosteroids also compete on the genomic level with the expression of Brain Derived Neuronal Factor (BDNF), thus interfering with the regeneration of neurons. Antidepressants, phenytoin, tianeptine benzodiazepines, NMDA antagonists and possibly calcium antagonists exert neuroprotective properties.



## Conclusions

Better understanding of neurodegeneration mediated by corticosteroids could bring new insight into the pathogenesis of mental disorders and stimulate novel diagnostic and therapeutic approaches. Endocrine evaluation and HPA activity assessment could become an important part of a diagnostic guideline and a tool for choosing the most appropriate treatment strategy for the respective patient. New pharmacotherapeutic modalities acting on specific GR or CRH receptors, or interacting with GABAergic, glutamatergic or serotonergic systems to prevent neurotoxic effects of corticosteroids, could emerge from this field of research.

Corticosteroids are widely used in the therapy of many somatic disorders. Nevertheless, their possible cognitive and neurodegenerative effects are not generally regarded. More detailed study of corticosteroid neurotoxicity could lead to the research of protective compounds preventing neurodegeneration as a side effect of the therapy with corticosteroids.

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