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GLUCO- AND MINERALOCORTICOID RECEPTOR REGULATION OF REGIONAL BRAIN NEUROTROPHISM

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Cover figure:

Photomicrographs showing double immunofluorescence labeling of GR-ir (FITC, green color) and GFAP-ir (Texas Red) in the CA1 region of the dorsal hippocampus of hormone-vehicle injected (propylene glycol, s.c., 1.5 h) SHAM (left), adrenalectomized (middle) and of corticosterone (10 mg/kg, s.c., 1.5 h) injected adrenalectomized (right) rats. Cellular co-localization is indicated by yellow color. CA1, Cornus Ammon area, Bregma level = -3.5 to -4.5 mm.

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To the memory of my mother

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Abstract

Gluco- and mineralocorticoid hormones exert powerful actions on brain function and are important in the mediation of the stress response and the survival of hippocampal neurons.
The aim of this thesis was to study the influence of glucocorticoid (GR)/mineralocorticoid receptor (MR) actions on brain neurotrophism including analyses of immediate early genes (IEGs) and of feedback responses on GR and/or MR. In order to independently study the acute effects of gluco- and mineralocorticoid hormones via GR and/or MR activation on gene expression levels the experimental animals were adrenalectomized (ADX) and thus depleted of all endogenous adrenal steroid hormones. Changes in hormonal levels appear to have profound effects on the expression of the neurotrophic factors while their receptors are only moderately affected. It was found that activated GR and MR act in concert or alone to mediate glucocorticoid hormone effect in various regions of the hippocampus. For example, GR and MR regulate basic fibroblast growth factor (bFGF) in CA2, CA3 and dentate gyrus together, but GR seems to act on bFGF alone in CA1 and CA4, suggesting that adrenal steroid hormones participate in the control of neurotrophic factor signaling in a highly subregion- and also cellular-dependent manner. The present thesis also shows that a depletion of adrenal steroid hormones after ADX may alter bFGF gene expression in the rat hippocampus through post-transcriptional rather than transcriptional mechanisms. However, evidence was also found that GR and MR activation might indeed involve onset of bFGF transcription.
In time course experiments for corticosterone action in ADX rats, differential responses in bFGF and brain-derived neurotrophic factor (BDNF) expression were found: bFGF mRNA levels were upregulated while BDNF mRNA and protein levels were downregulated. Peak effects on mRNA levels were found at 4 h for both genes. Because of the complexity of the BDNF promoter region the negative regulation of this gene by corticosterone was further analyzed by *in situ* hybridization with a number of exon-specific riboprobes. It appears that only the promoter II and especially the promoter IV are targets of the corticosterone effect.

The present thesis also shows that the effects of corticosterone on bFGF and BDNF expression are preceded by a downregulation of the Fos-family of inducible transcription factors. To study the function of *c-fos*, the transcriptionally most active member of the Fos-family, an antisense gene "knockdown" approach was developed. Using intrahippocampal administered *c-fos* antisense oligodeoxynucleotides, it was demonstrated that within the CA1 region *c-fos* seems to counteract the corticosterone effects on bFGF and BDNF expression.

It was also shown that besides the well-known negative feedback regulation of GR and MR gene expression by adrenal steroid hormones in the hippocampus, there exists a biphasic autoregulation of MR mRNA by aldosterone via activation of MR alone in the medial septal nucleus. These findings suggest a unique responsiveness to MR activation in this nucleus which may be of importance for the regulation of septo-hippocampal cholinergic pathways and thus of limbic circuits.

In summary, this thesis will help to define the role of brain GR and MR in neurotrophic responses, and thus in brain plasticity.

Keywords
Neurotrophins, BDNF, NT-3, bFGF, FGF receptor, immediate early genes, *c-fos*, antisense oligodeoxynucleotides, adrenalectomy, stress, glucocorticoids, mineralocorticoids, glucocorticoid receptor, mineralocorticoid, receptor *in situ* hybridization.

LIST OF PUBLICATIONS

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II. **A.C. Hansson**, A. Cintra, N. Belluardo, W. Sommer, M. Bhatnagar, M. Bader, D. Ganten, K. Fuxe. *Gluco- and mineralocorticoid receptor- mediated regulation of neurotrophic factor gene expression in the dorsal hippocampus and the neocortex of the rat*. Eur. J. Neurosci. 12(8): 2918-34, 2000.

III. **A.C. Hansson**, W. Sommer, B. Andbjer, M. Bader, D. Ganten, K. Fuxe. *Induction of hippocampal glial cells expressing basic fibroblast growth factor RNA by corticosterone*. NeuroReport 12(1): 141-145, 2001.

IV. **A.C. Hansson**, M. Metsis, W. Sommer, I. Strömberg, L.F. Agnati, K. Fuxe. *Corticosterone actions on the hippocampal BDNF expression are mediated by exon II and exon IV promoters*. Manuscript, 2002.

V. W. Sommer, R. Rimondini, W. O`Connor, **A.C. Hansson**, U. Ungerstedt, K. Fuxe. *Intrastriatally injected c-fos antisense oligonucleotide interferes with striatonigral but not striatopallidal γ-aminobutyric acid transmission in the conscious rat*. Proc. Natl. Acad. Sci. USA 93: 14134-14139, 1996.
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ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ADX	adrenalectomy
ALDO	aldosterone
AP-1	activator protein-1
AVP	arginine vasopressin
BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
CA1-CA4	Cornus of Ammon areas of the hippocampus
CBG	corticosterone-binding globulin
CREB	cyclic AMP response element binding protein
CORT	corticosterone
CRH	corticotrophin-releasing hormone
DEX	dexamethasone
DG	dentate gyrus
FGF-R1-3	fibroblast growth factor receptor subtypes 1-3
GFAP	glial fibrillary acidic protein
GABA	γ-aminobutyric acid
GR	glucocorticoid receptor
GRE	glucocorticoid response element
hsp	heat shock protein
HPA	hypothalamo-pituitary-adrenal
11β-HSD	11β-hydroxysteroid dehydrogenase
IEG	immediate early gene
LS	lateral septal nucleus
MR	mineralocorticoid receptor
MS	medial septal nucleus
NeuN	neuronal nuclei
NT-3	neurotrophin-3
ODN	oligodeoxynucleotide
PIT	pituitary
PLSD	protected least square difference test
PVN	hypothalamic paraventricular nucleus
RU 28362	synthetic glucocorticoid agonist

INTRODUCTION

1. Adrenal steroid hormones and their receptors

An important role for the cortex of the adrenal gland in maintaining vital functions was suggested nearly 150 years ago by Thomas Addison (1855). A soluble factor or hormone released by the adrenocortex was discovered and named "glucocorticoid" in the 1930s; "corticoid" since it was produced in the adrenal cortex and "gluco" for its effect in stimulating hepatic and renal gluconeogenesis (Long et al., 1940). In 1946, Hans Selye reported that some "diseases of adaptation" were caused by a hyperfunction of the adrenal gland in response to stress. He described the "general adaptation syndrome" via which all organisms respond to stress. The idea of an axis with adrenocorticotrophic hormone (ACTH) release from the pituitary, driving glucocorticoid secretion from the adrenal gland, was consolidated. Harris' description in 1955 and 1966 of the hypophyseal portal system opened up the way for a hypothalamic control of the adenohypophyseal hormones. The isolation of the 41-residue ovine hypothalamic peptide corticotrophin-releasing hormone (CRH), by Vale (1973), that stimulates the corticotrophs to release ACTH and β-endorphin made it possible to analyze the hypothalamic control of ACTH secretion in great detail. However, in 1984, Munck and co-workers suggested that in the absence of stress, glucocorticoids served primarily a permissive function, whereas during stress the major role of glucocorticoids was to modulate other adaptive responses and thereby prevent the host from overreacting. The most important role of glucocorticoids in an overall adaptive perspective is to (temporarily) shift priorities from long term to short term goals, as described by Sapolsky et al.(1986) and McEwen and Brinton (1987).

1.1.Synthesis and release of circulating adrenal steroids

The cortex of the adrenal gland synthesises glucocorticoids, mineralocorticoids and androgens. In rats and mice the primary glucocorticoid is corticosterone, which also functions as the mineralocorticoid (McNicol and Laidler, 1996), while the principal mineralocorticoid is aldosterone. Gluco- and mineralocorticoids are derived from cholesterol and are collectively referred to as corticosteroids or adrenal steroids. Through the action of different enzymes cholesterol is transformed into pregnenolone and progesterone to 11-deoxycorticosterone and finally to corticosterone, which can be converted further to aldosterone (White, 1994). Glucocorticoid secretion is dependent upon the release of ACTH from the anterior pituitary

gland (PIT/ant). ACTH synthesis and secretion are modified by corticotrophin-releasing hormone (CRH) in synergy with arginine vasopressin (AVP), angiotensin II and catecholamines. The binding of ACTH to its receptor increases the conversion of cholesterol to pregnenolone (Antoni, 1986). The subsequent rise in glucocorticoid levels exerts a negative feedback on the hypothalamus and pituitary by reducing the transcription of genes coding for CRH, AVP and ACTH. A drop in glucocorticoid levels stimulates ACTH release, and the cycle of feedback inhibition of ACTH by glucocorticoids continues (Bravo, 1989; Fig. 1). The release of glucocorticoids into the bloodstream shows a circadian pattern, with low levels during rest or sleep and high levels at the beginning of active periods. While ACTH can transiently increase aldosterone production, the major factors influencing aldosterone secretion are the renin-angiotensin system, extracellular sodium and potassium (Bravo, 1989).
Stressful stimuli produce a variety of physiological changes, including the activation of the hypothalamo-pituitary-adrenal (HPA) axis subserving an adaptive response towards the challenges facing the organism. However, prolonged glucocorticoid excess, resulting from either spontaneous (e.g. Cushing's disease, enduring HPA-axis activation) or therapeutic causes, may also be maladaptive, and has been suggested to play a role in the pathogenesis of neurodegenerative disorders as well as depression and posttraumatic stress disorders (PTSD, McEwen, 1999a). Aldosterone is mainly involved in the regulation of blood sodium and potassium levels and the extracellular fluid volume (Biglieri et al., 1994). The possible role of this mineralocorticoid in stress responses is less well known, but an interplay between gluco- and mineralocorticoid signaling has been suggested (see below). Molecular mechanisms involved in both gluco- and mineralocorticoid action are therefore of interest for a mechanistic understanding of adaptive as well as mal-adaptive stress responses, in particular in relation to neuronal survival and degeneration. An understanding of these mechanisms may also offer attractive novel treatment targets in related disease states.

1.2. Gluco- and mineralocorticoid receptors

Gluco- and mineralocorticoids may affect nerve cell function by increasing or decreasing the transcription of specific target genes via binding to intracellular hormone receptors. Two types of receptors have been identified: type I receptors, also known as mineralocorticoid receptors (MRs), which bind mineralocorticoids as well as glucocorticoids with high-affinity, and type II receptors, glucocorticoid receptors (GRs), preferentially binding glucocorticoids with low affinity and mineralocorticoids with a very low affinity (de Kloet & Reul, 1987; de Kloet, et al., 1994). GR mRNA and proteins are widely expressed in the rat brain with high

expression levels e.g. in regions involved in the feedback regulation of the hormonal stress response (Aronsson et al., 1988; Cintra et al., 1994). In contrast, MR shows a more restricted expression with high expression levels in the limbic system (McEwen et al., 1968; Arriza et al.1988, Herman et al., 1989). GR and MR are expressed in both neuronal and glial cells (Bohn et al., 1994; Cintra et al., 1994). Both types of receptors are highly prevalent in the hippocampus and are co-expressed within the majority of pyramidal and granular neurons (Eekelen & de Kloet, 1992; Fuxe et al., 1996b).

In normal rats, MR has a more than tenfold higher binding affinity (K_D) to corticosterone than to GR (MR: $K_D \approx 0.1$ - 0.3 nM, GR: $K_D \approx 5.0$ nM, Reul & de Kloet, 1985, Reul et al., 1990, 2000) with the consequence that MR is extensively occupied under basal conditions, while GR saturation requires hormone levels that occur after stress or after the circadian peak (Reul et al., 1987a, 1987b). Therefore, it has been proposed that MR regulates HPA axis activity under basal, and GR under stimulated, conditions (Reul et al., 2000). MR in the hippocampus inhibits basal HPA axis activity by influencing CRH and AVP secretion from the paraventricular nucleus of the hypothalamus (PVN), whereas hippocampal GR acts in the opposite way (Ratka et al., 1989; de Kloet et al., 1998, Fig. 1). In contrast, GR exerts inhibitory action in the PVN and the pituitary gland, which prevents an overreaction of the HPA axis under stress conditions and during the diurnal peak (see Fig. 1). Aldosterone has a 25-fold higher affinity for MR ($K_D \approx 0.1$ - 0.3 nM, Reul et al., 2000) than for GR and the levels of serum aldosterone are 100 to 1000 times less than the levels of serum corticosterone (Funder & Sheppard, 1987; McEwen, et al., 1986). The aldosterone selective binding to MR may mainly be due to two factors: the corticosterone-binding globulin (CBG, transcortin) and the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). The availability of circulating glucocorticoid concentrations to cells and tissues is regulated by CBG, which binds glucocorticoids exclusively with almost no affinity for aldosterone. In fact, the free glucocorticoid levels in blood serum constitute only a few percent (4 %) of the total hormone concentration. Under physiological conditions, 90 % of glucocorticoids are bound to CBG and the remainder is bound to albumin. In contrast, aldosterone binds weakly to CBG and circulates mostly bound to albumin. Free aldosterone comprises 30 – 50 % of its blood serum concentration (Biglieri et al., 1994). CBG is in turn subject to negative glucocorticoid regulation (Smith and Hammond, 1992). During a stressful situation, the levels of CBG are downregulated to approximately half of the normal level (Zouaghi et al., 1983; Purgeat et al., 1989) to expose cells and tissues to increased free concentrations of glucocorticoids and thus

with the ability to bind to their receptors. The amount of cellular glucocorticoids available to a specific receptor can by regulated by the presence of the enzyme 11β-HSD, which catalyses the conversion of active glucocorticoids to inert 11-keto-products (Funder et al., 1996; Seckl, 1997). Two isoforms of this enzyme are to be found, 11β-HSD type 1 and 11β-HSD type 2. In the adult brain, 11β-HSD type 1 is widely expressed and shows bidirectional activity, inactivating and regenerating glucocorticoids, while 11β-HSD type 2 has a very limited expression and exclusively inactivates glucocorticoids (Seckl, 1997).

The selective binding of aldosterone to MR can also be mediated by the activity of an enzyme, aldosterone synthase, which gives rise to higher concentrations of intracellular aldosterone (MacKenzie et al., 2000a, 2000b; Yu et al., 2002).

The hormone sensitivity of GR and/or MR can be changed by alterations in levels and compositions of heat shock proteins (hsp), which are associated with non-liganded receptors and thereby facilitate the steroid ligand-binding to its receptor (Picard et al., 1990). It has been shown that hsp70 and hsp90 are targets for glucocorticoid regulation (McGuire et al., 1992, Patchev et al., 1994; Udelsman et al., 1994), and consequently may affect the binding of the steroid to its receptor and thus the activity of GR and/or MR.

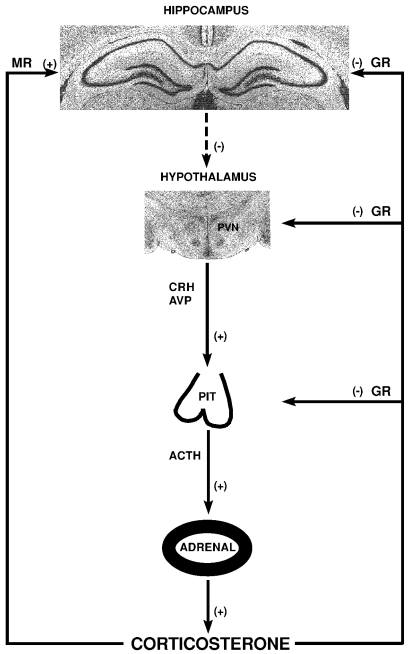

Figure 1
Regulation of the hypothalamo-pituitary-adrenal (HPA) axis by GR and MR. MRs mediate potentiation of hippocampal output, and thus enhance neural inhibition of HPA axis, while GRs reduce hippocampal output, which leads to HPA disinhibition. GRs in hypothalamic paraventricular nucleus (PVN) and pituitary (PIT) mediate negative feedback action of corticosterone on HPA activation. (Adapted from de Kloet et al., 1998).

1.3. Gene regulation by GR and MR

Gluco- and mineralocorticoids exert their effects through intracellular GR or MR, which are primarily located in the cytoplasm in the inactive state. Upon binding of the hormone, the receptor undergoes a conformational change leading to the release of various molecular chaperones (e.g. hsp90, hsp70, hsp56) associated with the non-liganded receptor (Pratt and Toft, 1997). The activated receptor translocates to the nucleus and can bind as a homo- or heterodimer to specific DNA sequences, the glucocorticoid response elements (GRE, consensus sequence: 5'-AGAACAnnnTGTTCT-3'). GR/MR binding to GRE can alter the rate of transcription, resulting in either its induction or repression (Ou et al., 2001). Since the description of the classical GRE consensus sequence a number of novel GREs have been discovered including exclusively positive or negative acting GREs (Akerblom & Lellon, 1991; Drouin, 1993) and binding sites for MR/GR homo-/heterodimers on 'composite' elements with overlapping binding sites for other transcription factors, e.g. activator protein-1 (AP-1) complex (Diamond et al., 1990; Funder, 1993; Pearce and Yamamoto, 1993).

GR and MR binding to DNA is not always necessary for altering gene expression. GR can indirectly change gene expression via protein-protein interaction with transcription factors (e.g. AP-1, nuclear factor-kB, NF-kB, Schüle et al., 1990; Yang-Yen et al., 1990; König et al., 1992). A repression of AP-1 and NF-kB activity by glucocorticoids has been described in tissue culture studies (Diamond et al., 1990, Jonat et al, 1990, Lucibello et al., 1990; Schüle et al., 1990; Yang-Yen et al., 1990; Heck et al., 1994; Karin and Chang, 2001), and it has been suggested that interaction of GR with Jun/Fos heterodimers leads to reduced AP-1 activity, whereas interaction with Jun homodimers leads to enhanced AP-1 activity (Teurich and Angel, 1995). Evidence for such a transcriptional transrepression of AP-1 and GR was also recently shown *in vivo* by a specific knock-in mutant mouse strain $GR^{dim/dim}$, whose GR is unable to bind with high affinity to GRE due to defective dimerization but is still fully capable of repressing AP-1 and NF-κB activities (Reichardt et al., 1998). Also, glucocorticoids can reduce the Jun N-terminal kinase activity (Caelles et al, 1997) and thereby reduce the activity of transcription factors, involved in the induction of fos and jun gene transcription, as well as reducing the transcriptional activity of Jun heteromeric complexes (Karin and Chang, 2001).

1.4. Feedback regulation of GR and MR

Glucocorticoids play an important role in mediating the stress response in the brain. An important part in the stress response is the negative feedback regulation of GR and MR. Increased hormone binding exerts inhibitory actions on GR and MR biosynthesis/availability (i.e., "desensitization"), whereas decreased hormone availability increases receptor number. ADX-induced hormone depletion elicits a rise in the number of adrenal steroid receptors (Tornello et al., 1982, Sarrieau et al., 1986; Chao et al., 1989; Herman et al., 1989; Luttge et al., 1989; Spencer et al., 1991; Miller et al., 1992; Herman, 1993) and the number of these receptors is significantly downregulated upon administration of high doses of glucocorticoids (dexamethasone or corticosterone) or under conditions where circulating glucocorticoids are chronically elevated (Reul et al, 1987a,b; Sapolsky et al, 1984; Sapolsky & McEwen, 1985). The mechanism by which gluco- and mineralocorticoids regulate their own receptor is complex and appears not to be easily defined. Feedback regulation of GR and MR may be mediated at several levels: (1) the transcriptional level as evidenced by the ability of hormone-receptor complexes to up- or downregulate the rate of receptor gene transcription (Rosewicz et al., 1988; O'Donnell & Meaney, 1994; Meyer & Schmidt, 1995); (2) the post-transcriptional level as evidenced by the ability of ligands to alter the stability of their own receptor message (Meyer & Schmidt, 1995; Paskitti et al., 2000; Verrey et al., 2000); and by the ability of agonists to change the half-life of their own receptor protein (McIntyre & Samuels, 1985).

The hippocampus contains high densities of GR and MR and is a region where both receptors are predominantly regulated by negative feedback. The hippocampus is furthermore thought to exert a tonic inhibitory control on HPA activity (Herman et al., 1995; de Kloet, 1998). Disturbance of this negative feedback through hippocampal damage or cell loss can result in the pathogeneses of stress-related disorders in humans (de Kloet et al., 1998; McEwen, 1999a; Holsboer, 2001).

1.5. Acute effects of glucocorticoids on brain plasticity

The acute effects of glucocorticoids are mediated by a direct influence on neuronal excitability and plasticity (de Kloet, 1999). In the hippocampus, a particularly vulnerable and sensitive region of the brain important for declarative and spatial learning and memory (Eichenbaum, 1997), low levels of glucocorticoids increase neuronal excitability by mainly activating MR and high levels of glucocorticoids inhibit neuronal excitability by activating both GR and MR (Joëls & de Kloet, 1992). A similar observation was made for neuronal

plasticity. Activation of mainly MR will favor the activation of long-term potentiation (LTP), whereas additional activation of GR will suppress LTP and favor long-term depression (LTD, Pavlides et al., 1995; Pavlides & McEwen, 1999). Changes in synaptic plasticity such as LTP and LTD are proposed to underlie learning processes. By affecting synaptic plasticity, GR and MR may modulate learning and memory. In fact, pharmacological experiments indicate that an activation of GR facilitates memory consolidation, whereas MR activation alone is beneficial through the modulation of attention or behavioral reactivity (Oitzl & de Kloet, 1992; Oitzl et al., 1994; Conrad et al., 1999).

1.6. Chronic effects of glucocorticoids on brain plasticity

Prolonged exposure to glucocorticoids or chronic stress leads to decreased neurogenesis and atrophy, with damage or death of hippocampal pyramidal neurons, which is associated with cognitive impairments (Lupien et al., 1998; McEwen, 1999a,b). High levels of glucocorticoids damage mainly the CA3 region of the hippocampus, while the CA1 and the dentate gyrus are less affected (Sapolsky et al., 1986; Sapolsky, 1992). This pattern of hippocampal damage correlates to that seen in the normal aged hippocampus: a decrease in the number of pyramidal neurons especially in the CA3, a loss of GR/MR and high levels of astrogliosis (McEwen, 1999b, Nichols et al., 2001). Glucocorticoid-induced cell death is generally believed to be apoptotic (Sapolsky, 1996; Reagan & McEwen, 1997; McEwen, 1999a). In contrast, removal of gluco- and mineralocorticoids by ADX has important consequences for morphology most notable in the dentate gyrus of the hippocampus (Cameron & Gould, 1994). Both production and degeneration of dentate gyrus cells were found to be accelerated in the absence of hormones (Sloviter et al., 1989, 1993; Gould et al., 1990, 1991; Sapolsky et al., 1991; Jaarsma et al., 1992; Cameron & Gould, 1994). ADX-mediated cell death in the dentate gyrus can be prevented by administration of low doses of corticosterone sufficient to occupy MR (Landfield et al., 1981; Sloviter et al., 1989; 1993, Woolley et al., 1991; Hu et al., 1997; Stienstra et al., 1998). In support of this, adult MR knock out mice display a reduction of dentate gyrus cells similar to that observed after ADX and show reduced neurogenesis, which may be an indirect effect of GR activation due to their elevated serum corticosterone levels (Gass et al., 2000).

Several mechanisms could contribute to the atrophy and loss of neurons found in response to stress. One possibility is that stress and glucocorticoids damage certain populations of stress-vulnerable neurons (Sapolsky, 1996; McEwen, 1999a). These studies demonstrate a role for glutamate excitoxicity and a reduction in metabolic capacity, which result from a reduction in

glucose uptake. Another possibility is that these effects could produce a state of neuroendangerment whereby cells become more vulnerable to other types of insult, such as hypoxia-ischemia, hypoglycemia, or viral infection. Stress or glucocorticoids decrease neurogenesis of granule cells in the DG by yet unknown mechanisms, although there is increasing evidence that neurotrophic factors, e.g. basic fibroblast growth factor (bFGF), regulate neurogenesis of hippocampal granule neurons in adult animals (Cheng et al., 2002). Furthermore, high levels of circulating adrenal steroid levels or stress have been reported to regulate the expression of neurotrophic factor genes in the adult hippocampus (e.g. a decrease of brain-derived neurotrophic factor, BDNF; an increases of bFGF and neurotrophin-3, NT-3), which can lead to a loss of normal plasticity and eventually damage and loss of neurons.

2. Neurotrophic factors

The origin of the present conception of neurotrophic factors in brain plasticity can be found in experiments on development of the chick nervous system about 70 years ago. Hamburger (1934) demonstrated that the survival of chick sensory neurons innervating the developing limb buds was highly dependent on the target tissue. Some years later Brücker (1948) observed that after transplantation of mouse sarcomas into chick embryos the tumor tissue was innervated by host sensory neurons. This biological activity was ascribed to a soluble protein, which was then purified and characterized as nerve growth factor (NGF, Levi-Montalcini & Hamburger, 1953; Cohen et al., 1954). These findings led to the establishment of NGF's crucial role in the development of peripheral and sympathetic neurons and of basal forebrain cholinergic neurons (Levi-Montalcini & Angeletti, 1968; Thoenen & Barde, 1989; Thoenen et al., 1987; Whittemore & Seiger, 1987; Hefti et al., 1989). Later, other neurotrophic factors were isolated and characterized. The molecular cloning of BDNF (Leibrock et al., 1989) demonstrated that the BDNF protein has about 50 % amino acid similarity to NGF. Based on this sequence similarity, additional members of the NGF family, collectively referred to as neurotrophins, were identified (Ernfors et al., 1990; Hohn et al., 1990; Jones & Reichardt, 1990; Maisonpierre et al., 1990a; Rosenthal et al., 1990; Kaisho et al., 1990).

A number of additional growth factors have been found to regulate neuronal survival and are consequently considered as neurotrophic factors. This group of molecules includes the fibroblast growth factor family (FGFs, Morrison et al., 1986; Walicke et al., 1986; Walicke & Baird, 1991). FGF was originally purified from the bovine pituitary gland as a mitogen that could stimulate the growth of cultured cells (Gospodarowicz & Handley, 1975;

Gospodarowicz & Moran, 1975; Jones & Addison, 1975). Over the past few years 22 members of the FGF family sharing 13 % to 71 % amino acid identity have been isolated from vertebrates (Ornitz, 2000; Ornitz & Itoh, 2001). FGFs have a high affinity for heparan sulfate proteoglycans and require heparan sulfate to activate one of the five cell-surface FGF receptors (Lin et al., 1999; Sleeman et al., 2001). During development, FGFs have diverse roles in regulating cell proliferation, migration and differentiation. In the adult organism, FGFs are homeostatic factors and function in tissue repair. When inappropriately expressed, some FGFs can contribute to tumor development. About ten members of the FGF-family, among them basic FGF (bFGF or FGF-2), are expressed in adult nervous tissue and are inter alia important for neuronal signal transduction in the central and peripheral nervous systems (Ornitz, 2000; Ornitz & Itoh, 2001).

Neurotrophic factors exert a variety of effects in the nervous system. They are typically secreted proteins that bind to and activate cell-surface tyrosine kinase coupled receptors, leading to induction of phosphorylation cascades and transcription factor activation with effects on gene expression. Neurotrophic factors are crucial for early nerve cell development in regulating proliferation, differentiation, survival and target finding (Barde, 1994; Lindsay, 1994; Ibanez, 1998). In the adult CNS they may be important for establishment, maintenance and plasticity of synaptic connections (Beck, 1994; McAllister et al., 1999). The functions of neurotrophic factors in the hippocampus may include involvement in long-term potentiation and plasticity (Marty et al., 1997), influences on mood (Duman et al., 1997), neurogenesis (Collazo et al., 1992) and neuroprotection (Beck et al., 1994).

2.1. Neurotrophins

Neurotrophins play an important role in the survival and differentiation of neurons (Levin & Barde, 1996). They influence the development and shaping of the nervous system by supporting the survival of some but not all neurons (McAllister et al., 1999). BDNF and NT-3 seem to be produced in an activity-dependent manner, indicating their role in neuronal plasticity (Hughes et al., 1993; Kang & Schuman, 1995; McAllister et al., 1999). Moreover, BDNF and, to a lesser extent, NT-3 have also been shown to directly elicit action potentials in the brain (Kafitz et al., 1999). BDNF have been implicated in the induction of LTP (Castrén et al., 1993), BDNF, but not NT-3, mRNA increases following the induction of LTP (Kang & Schuman, 1995) and there is an apparent impairment of LTP in rats which lack BDNF (Korte et al., 1995). A role of NT-3 in spatial learning appears to be well established (Fisher et al., 1994; Pelleymounter et al., 1996). However, there is conflicting evidence for the requirements

of BDNF in spatial learning (Fisher et al., 1994; Linnarsson et al., 1997; Ma et al., 1998). Studies examining the effects of antisense oligodeoxynucleotides (ODN) directed against BDNF expression, as well as some studies using BDNF null mutant mice, suggest that BDNF is important for spatial learning (Linnarsson et al., 1997), while others suggest that is not (Montkowsky et al., 1997). In contrast, in emotional tasks it seems that BDNF but not NT-3 seems to be important for memory consolidation, as demonstrated in the passive avoidance test for chicken by using antisense ODN injection to block BDNF and NT-3 expression (Johnston & Rose, 2001). Finally, infusions of either BDNF or NT-3 have been shown to alter exploratory behaviors and sleep patterns in rats (Martin-Iverson & Altar, 1996).

BDNF and NT-3 are synthesized as preproproteins of similar sizes that are cleaved and released to mature proteins. They may derive from presynaptic, as well as from postsynaptic sites and have shown to modulate both pre- and postsynaptic transmission (Poo, 2001, Kovalchuk et al., 2002; Manabe, 2002). BDNF and NT-3 binding to their high-affinity tyrosine kinase receptors (trkB, trkC) leads to the activation of multiple signaling pathways, promoting survival through the PI3K pathway, differentiation and neurite growth through Ras/MEK/MAPK and activity-dependent plasticity through PLCγ-induced extracellular calcium influx (Bibel & Barde, 2000). BDNF and NT-3 are secreted by an activity-dependent pathway that depends on release of calcium from intracellular stores (Griesbeck et al., 1999; Höner, 2000; Wang et al., 2002) and are sensitive to specific temporal patterns of activity (Balkowiec & Katz, 2000).

BDNF expression is found in neurons throughout the brain with highest levels in the hippocampus and the cerebral cortex (Hofer et al., 1990; Phillips et al., 1990; Wetmore et al., 1990), while NT-3 mRNA shows a restricted distribution with clearly higher levels in neurons of the hippocampus and the cerebellum compared to other areas of the brain (Ernfors et al., 1990; Hohn et al., 1990; Maisonpierre et al., 1990a,b; Phillips et al., 1990). Generally, expression of NT-3 is highest in immature CNS and dramatically decreases with maturation. In contrast, expression of BDNF is low in developing regions of the CNS and increases as these regions mature (Maisonpierre et al., 1990b; Friedman, 1991; Timmusk et al., 1993, 1994a). In the adult brain, BDNF and NT-3 expression in the brain are modulated by physiological activity. After neuronal activity, BDNF expression is upregulated and NT-3 expression is downregulated in the hippocampus (Lindvall et al.,1992; Rocamora et al., 1992, Timmusk et al., 1994b; Bengzon et al., 1993). The activity-dependent upregulation of BDNF mRNA involves direct onset on transcription, which is dependent on calcium entry and activation of the transcription factor CREB (Timmusk et al, 1995; Shieh et al., 1998; Tao et

al., 1998; McAllister et al., 1999). Interestingly, in the hippocampus of subjects with Alzheimer's disease BDNF is decreased (Phillips et al, 1991) and it has been suggested that BDNF contributes to the pathogenesis of Alzheimer's disease (Siegel & Chauhan, 2000).

2.2. Basic Fibroblast Growth Factor

bFGF is the best characterized member of the FGF protein family. This factor has a critical trophic role in a variety of neuronal cell types (Anderson et al., 1988; Perraud et al., 1988; Walicke, 1986; Grothe et al., 1989; Ferrari et al., 1989; Knüsel et al., 1990; Gomez-Pinilla et al., 1992, 1995a; Peterson et al., 1996) and promotes proliferation or reactivity of astrocytes (Perraud et al., 1988; Gomez-Pinilla, 1995a). Addition of bFGF to cultured astrocytes induces synthesis and secretion of NGF and most likely other trophic factors (Fukumoto et al., 1991; Yoshida & Gage, 1991; Gaul & Lubbert, 1992). Recently, bFGF knockout mice, which are viable, fertile and apparently normal, showed a reduction in the neuronal density in the motor cortex, whereas cell density in other brain regions such as hippocampus appeared normal (Ortega et al., 1998). This suggests that bFGF controls *in vivo* migration, differentiation and survival especially of cortical neurons (Dono et al., 1998). Other studies indicate that bFGF is regulated in an activity-dependent fashion (Gomez-Pinilla, 1995b, 1997, 1998), raising the possibility that bFGF is involved in behavioral function. It has been shown that bFGF enhances long-term potentiation (LTP) in hippocampal slices (Abe et al., 1990; Terlau & Seifert, 1990) and in anaesthetized rats (Ishiyama et al., 1991), promotes synaptogenesis in cultured cells (Peng et al., 1991) and modulates synaptic transmission in the rat hippocampus (Abe et al., 1990; Tanaka et al., 1996). Since hippocampal LTP is considered to be a cellular basis of learning and memory (Bliss & Richter-Levin, 1993), bFGF may affect learning and memory. bFGF can also activate the transcription factor CREB that is essential for memory function (Ginty et al., 1994) and infusion of bFGF into the brain has been shown to facilitate spatial learning (Ishihara et al., 1992; Wen et al., 1995; Abe & Saito, 2001).

Many of the biological activities of bFGF have been found to depend on its receptors' intrinsic tyrosine kinase activity and its downstream second messenger system. The neurotrophic effect of bFGF is mediated by the MAPK signal transduction cascade (Abe & Saito, 2001; Lenz et al., 2001). In contrast to the other FGFs, bFGF does not contain hydrophobic signal sequences believed to be necessary for secretion (Baird, 1994). It has been suggested that bFGF can be released from damaged cells or by an exocytotic mechanism that is independent of the endoplasmatic reticulum-trans golgi network pathway (Mignatti et al., 1991). Once on the surface, bFGF can bind to its low- and high-affinity receptors. This may

induce neighboring cells to produce growth factors, which then can act back on cells. Four FGF receptors (FGF-R1 to -R4) containing an intracellular tyrosine kinase domain and a number of variants have been characterized, with FGF-R1 to -R4 binding bFGF with distinct affinities (Ornitz et al., 1996). Recently, a novel FGF receptor (FGF-R5) was isolated from murine lymphatic tissue. This receptor binds bFGF and is expressed in all tissues with higher levels in the brain, kidney and liver (Sleeman et al., 2001). In addition to the FGF high-affinity receptors, a transmembrane proteoglycan containing heparan sulfate side chains binds bFGF with low-affinity (Kiefer et al., 1990). It has been established that heparan sulfate is required for FGFs to effectively activate FGF receptors (Rapraeger et al., 1991; Yayon et al., 1991; Ornitz et al., 1992; Lin et al., 1999). These interactions seem to stabilize the FGF-FGF receptor complex and may severely limit the diffusion of FGFs. Tissue-specific heparan fragments of defined sequence may differentially regulate FGF signaling by controlling FGF diffusion in the extracellular matrix and their ability to activate their receptors (Chang et al., 2000, Ornitz & Itoh, 2001).

bFGF is widely expressed in the brain and spinal cord, by astrocytes and neuronal subpopulations with an accumulation of bFGF mRNA and protein in the cytoplasm or in the nucleus (Emoto et al., 1989; Powell et al., 1991; Gomez-Pinilla et al., 1992; Matsuyama et al., 1992; Woodward et al., 1992; Fuxe et al., 1996a). bFGF tissue levels increase gradually during development towards adult levels. bFGF is encoded by a single copy gene which includes two introns and large 5' and 3' untranslated regions (UTR), suggesting an important regulation of its expression. A bidirectional transcription of the gene gives rise to multiple polyadenylated mRNAs from a single transcription start site (Stachowiak et al., 1994), as well as a 1.5 kb antisense transcript (gfg) which is complementary to the 3' untranslated region of the bFGF mRNA (Murphy & Knee, 1994). This antisense RNA has been implicated in the transcriptional and post-transcriptional regulation of bFGF expression and contains a long open reading frame encoding a functional nuclear protein with nucleotide hydroxylase enzymatic activity (Li et.al., 1996), which seems to be expressed in the pituitary (Asa et al., 2001) but is not detectable in the adult rat hippocampus by *in situ* hybridization (A.C. Hansson, unpublished observations). bFGF expression is regulated both at the transcriptional level and more importantly at the post-transcriptional level via mRNA polyadenylation, stability, and/or translation initiation (Murphy et al., 1990; Moffett et al., 1998; Touriol et al., 1999).

The levels of endogenous bFGF expression in the brain are increased or decreased in pathological conditions or neurodegenerative disorders. bFGF expression is increased in brain

regions following brain lesions (Anderson et al., 1988; Gomez-Pinilla et al., 1992; Miyamoto et al., 1993), ischemia (Nakata et al., 1993; Sakaki et al., 1995), or after excitoxic damage in the hippocampus (Liu et al., 1993). bFGF is also increased in patients suffering from Alzheimer's disease (Stopa et al., 1990; Gomez-Pinilla et al., 1990) and is decreased in patients with parkinsonian symptoms (Tooyama et al., 1993; Siegel & Chauhan, 2000), indicating that bFGF is involved in the neuroplastic processes of these diseases.

3. Possible links between adrenal steroids, neurotrophic factors and stress-related disorders

A critical role for GR and MR exists in CNS disease processes and aging. Chronic stress negatively influences cognitive performances (McEwen & Sapolsky, 1995; McEwen, 1999a). Long-term treatment of patients with glucocorticoids and chronically increased glucocorticoid levels in patients with Cushing's syndrome are associated with cognitive dysfunction, including memory deficits. Chronically increased glucocorticoid levels in aged rats and humans correlate with a decreased hippocampal volume and memory deficits (Lupien et al., 1998). This has also been found in psychosocially stressed tree shrews (Fuchs & Flugge, 1998, 2002) and it seems that the reduction in hippocampal volume reflects more reversible changes in dendritic atrophy or a shift in the water volume than cell loss (Fuchs & Flugge, 1998, 2002; McEwen, 1999a; Lucassen et al., 2001). Interestingly, treatment with the tricyclic antidepressant tianeptine counteracted the stress-induced reduction in hippocampal volume in psychosocially stressed tree shrews (Czeh et al., 2001). Psychiatric disorders such as depression are associated with a chronic upregulation of HPA axis activity and increased glucocorticoids levels (Barden et al., 1995; Holsboer, 2000; Pariante & Miller, 2001). Sustained increases of glucocorticoids raises anxiety levels, whereas inhibition of glucocorticoid synthesis or blockade of GR activity reduces anxiety (Korte et al., 1995, 2001; Roozendaal et al., 1996; Calvo & Volosin, 2001), again suggesting a role of central GR in emotional behavior. These facts have lead to the postulation of a relationship between brain GR/MR activity, and clinical depression (Brady et al., 1991; Pepin et al., 1992; Seckl & Fink, 1991; Barden et al., 1995; Holsboer, 2000). Further evidence linking neurotrophic factors to depression comes from studies with stress models, showing a decrease of BDNF expression and an increase of bFGF expression in the hippocampus. Chronic treatment of animals with antidepressants can prevent stress-induced reduction of BDNF mRNA and induce the expression of bFGF mRNA (Vaidya & Duman, 2001; Mallei et al., 2002). Moreover, BDNF promotes sprouting of injured serotonergic neurons and causes a substantial increase in

serotonergic terminal density in the neocortex (Mamounas et al., 2000). In addition, BDNF knockout mice show impaired serotonergic function (Lyons et al., 1999), indicating that neurotrophic factors might be a potential therapy for psychiatric illness characterized by sensitivity to serotonergic compounds (Duman et a., 1997).

AIMS OF THE THESIS

1. To study the influence of gluco- and mineralocorticoid receptor actions on the regional expression of neurotrophic factors and their receptors in the brain (Papers I, II, III, IV and VI).

2. To study the adrenal steroid hormone control of immediate early genes and their involvement, especially *c-fos*, in neurotrophic responses to gluco- and mineralocorticoid receptor activation (Papers V and VI).

3. To study the adrenal steroid hormone feedback responses of gluco- and mineralocorticoid receptors in tel- and diencephalic brain regions related to the regulation of the hypothalamo-hypophyseal-adrenal axis (Papers II, VI and VII).

MATERIAL AND METHODS

The following methods have been used (for details, see methods sections of individual papers):

Animal surgery

Bilateral adrenalectomy (*Papers II to VII*)

Stereotaxic operations (*Papers V and VI*)

Tissue dissection (*Paper IV and V*)

Pharmacological treatments

Hormones were solved in propylene glycol and subcutaneously administered 24 h after ADX (*Papers II to VII*):

- corticosterone (2 and 10 mg/kg)
- aldosterone (0.01 and 0.5 mg/kg)
- synthetic glucocorticoid agonist RU 28362 (4 mg/kg)

Oligodeoxynucleotides were solved in Ringer and infused into the respective brain region via intracerebral implanted cannula guides (*Papers V and VI*)

In vivo microdialysis (*Paper V*)

Molecular biology methods

All molecular biology procedures were performed according to standard practices (Sambrook et al., 1989):

Plasmid isolation, RNA isolation, RNA and protein preparation from tissue, polymerase chain reaction (PCR), reverse transcriptase (RT)-PCR, DNA subcloning, colony screening, DNA sequencing, labeling of DNA and RNA probes (*Papers I to VII*)

RNase protection assay (*Paper V*)

In situ hybridization

Riboprobe *in situ* hybridization (*Papers I to IV, VI and VII*)

Combined *in situ* hybridization with immunostaining (*Paper IV*)

Table 1. Riboprobes used for RNase protection assay and *in situ* hybridization.

gene	plasmid/vector	riboprobe length	cDNA	reference
rat BDNF				
exon I	pBluescript II KS$^+$	650 nt	Bam HI/Sac I-fragment	[d] gift from Dr. M. Metsis, Timmusk et al., 1993
exon II	pBluescript II KS$^+$	500 nt	Sca I/Hind III-fragment	[d] gift from Dr. M. Metsis, Timmusk et al., 1993
exon III	pBluescript II KS$^+$	400 nt	Eco RI/Xba I-fragment	[d] gift from Dr. M. Metsis, Timmusk et al., 1993
exon IV	pBluescript II KS$^+$	500 nt	Pvu II/Bam HI-fragment	[d] gift from Dr. M. Metsis, Timmusk et al., 1993
exon V	pBluescript II KS$^+$	350 nt	Pvu II/Pst I-fragment	[b,d,f] gift from Dr. M. Metsis, Timmusk et al., 1993
rat NT-3	pBluescript II KS$^+$	320 nt	Eco RV/Sca I-fragment	[b] gift from Dr. M. Metsis, Ernfors et al., 1990
rat bFGF	PCR-fragment	218 nt	cDNA: 442–660 bp	[b,c] made in our lab, El-Husseini et al., 1992
rat bFGF	pBluescript II SK$^+$	479 nt	Sma I/Xho I-fragment cDNA: 525-1004 bp	[f] gift from Dr. M. Blum, Bean et al., 1993
rat (gfg) bFGF	PCR-fragment	127 nt	cDNA: 1269-1142 bp	made in our lab, El-Husseini et al., 1992
rat FGF-R1	pBluescript II KS$^+$	220 nt	3'-part of non-coding sequence	[a,b] gift from Dr. P. Lonai, Safran et al., 1990
rat FGF-R2	pBluescript II KS$^+$	281 nt	cDNA: 121-402 bp	[a,b] gift from Dr. P. Lonai, Raz et al., 1991
rat FGF-R3	pBluescript II KS$^+$	430 nt	cDNA: 1233-1663 bp	[a,b] gift from Dr. D. Ornitz, Ornitz & Leder, 1992
rat FGF-R4	pGEM 3Zf(+)	1000 nt	1 kb Eco RI-fragment,	[a] gift from Dr. K. Alitalo, Korhonen et al., 1992
rat GR	pSP64	673 nt	Eco RI/Pst I-fragment, cDNA: 1691- 2364 bp	[b,f,g] gift from Dr. S. Okret, Okret et al., 1986
rat MR	pGEM 4	501 nt	Eco RI-fragment from 5'-part of coding sequence	[b,f,g] Arriza et al., 1987
rat c-fos	pBluescript II KS$^+$	557 nt	Bgl II/Stu I-fragment	[e,f] cDNA from Dr. J. Morgan, Curran et al., 1987
mouse fosB	pBluescript II KS$^+$	1704 nt	1.7 kb Bam HI/Pst I-fragment,	cDNA from Dr. J. Morgan, Zerial et al., 1989
rat fra-1	pGEM 4	1663 nt	1.6 kb Eco RI-fragment,	cDNA from Dr. J. Morgan, Cohen & Duran, 1988
mouse junB	pBluescript II KS$^+$	474 nt	Bam HI/Sac I-fragment, cDNA: 926-1463 bp	[e] cDNA from Dr. M. Yaniv, Ryder et al., 1988
mouse c-jun	pBluescript II KS$^+$	180 nt	Hind III/Pst I-fragment from 3' non-coding sequence	gift from Dr. M. Yaniv, Lamph et al., 1988
rat NGFI-A	pBluescript II KS$^+$	467 nt	Sph I/Avr II-fragment	[e] cDNA from Dr. N. Norton, Changelion et al., 1989
rat β-actin	pBluescript II SK$^+$	150 nt	Xba I/Sal I-fragment	[e] gift from Dr. M. Bader, Djavidani et al., 1995

[a] *paper I*, [b] *paper II*, [c] *paper III*, [d] *paper IV*, [e] *paper V*, [f] *paper VI*, [g] *paper VII*

Immunohistochemistry

Avidin-biotin-peroxidase complex immunostaining (*Paper IV*)

Double fluorescence immunostaining (*Paper IV and VI*)

Table 2. List of antibodies used for immunocytochemistry

antigen	raised in	dilution	paper
BDNF	rabbit	1 : 200	IV
GR	mouse	1 : 200	IV, VI
c-fos	rabbit	1 : 300	VI
CREB	rabbit	1 : 800	IV
pCREB	rabbit	1 : 800	IV
NeuN	mouse	1 : 200	VI
GFAP	mouse	1 : 200	IV, VI

Protein measurements

Enzyme linked immunoassay system (ELISA, *Paper IV*)

Protein measurements after *Lowry* (*Paper IV*)

Radioimmunoassay for corticosterone and aldosterone (*Papers II to IV, VI and VII*)

Neurotransmitter analysis

Reverse-phase HPLC (*Paper V*)

Data and statistical analysis

Data were obtained by semi-quantitative measurements of RNA or protein from brain section or of RNA on membrane using an image analyzing system (SAS Biovision image analyzing system, Avanzati, Milan, Italy, *Papers I to IV, VI and VII*), an automatic image analyzer (IBAS, Zeiss Kontron, Munich, Germany, *Paper IV*), a PC-based image analysis software system (Scion Image, Scion Corporation, Frederick, Maryland, *Paper IV*) or a phosphoimager (BAS-1500; Fuji, *PaperV*). Data were presented as means ± S.E.M. Statistcal analysis was performed by two-way ANOVA or by one-way ANOVA followed by Fisher's PLSD post-hoc test and Bonferroni's correction (*Papers I to III, VI and VI*) or Holm's improved weighted Bonferroni procedure (Holm, 1979, *PaperIV*). Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Paper I provides a detailed comparative analysis of rat brain regions that express transcripts coding for high-affinity FGF receptor subtypes FGF-R1, FGF-R2 and FGF-R3. It seems that FGF-R1 to -R3 are widely expressed but with region- and cellular specificity in the brain, indicating their differential role in brain neurotrophism. The mRNA of the fourth subtype (FGF-R4) was not detectable with the present methodology. Moreover, it seems to be exclusively expressed in the medial habenula nucleus in the adult rat brain (Itoh et al., 1994). FGF-R1 mRNA was found mainly in large cells most likely representing neuronal cell populations, which is in concordance with Asai et al. (1993) and Yazaki et al. (1994). In contrast, FGF-R2 mRNA was found primarily in small cells that could represent glial cells and less frequently in large neuronal cells. In addition, a distinct feature of FGF-R2 mRNA was expressed in the white matter, where only non-neuronal cells such as oligodendrocytes were present. FGF-R1 and R3 mRNAs were undetectable in the white matter. FGF-R3 mRNA was expressed only in a subset of small cells with a scattered distribution, and its neuronal or glial origin remains to be determined.

In the hippocampus, high levels of FGF-R1 mRNA were found in neuronal pyramidal cells, but with regional differences in labeling intensity. FGF-R2 mRNA labeling was found in pyramidal cell layers with low intensity. FGF-R3 showed a weak labeling in small, scattered cells within the pyramidal and granular cell layers of the hippocampus. Thus, it appears to exist an overlap between the differential cellular distribution of FGF receptor subtypes and their putative FGF ligands in several brain regions. In the hippocampal formation of adult animals bFGF (FGF-2, Emoto et al., 1989; Powell et al., 1991; Woodward et al., 1992; Fuxe et al., 1996), FGF-5 (Haub et al., 1990; Gomez-Pinilla, 1993), FGF-9 (Tagashira et al., 1995) and FGF-10 (Hattori et al., 1997) transcripts and most of their corresponding proteins correlate with high levels of the FGF-R1 mRNA (Asai et al., 1993; Yazaki et al., 1994; Gonzalez et al., 1995). FGFs may exert part of their trophic function in an autocrine-paracrine manner, involving neuronal, neuronal/glial, and glial/glial interaction (Fuxe et al., 1994).

Characterization of the ADX animal model

Throughout the remainder of the study, acutely ADX rats were used. Since the occupancy of GR and MR is primarily determined by circulating hormone levels, ADX rats were used, which are depleted of all adrenal steroids, to independently study the acute effects of gluco- and mineralocorticoids on gene expression via activation of GR and/or MR. For reasons of

comparability between the different experiments, the ADX animal model is described and discussed jointly for ***Papers II - VII***. Serum corticosterone and aldosterone levels from the different experiments are compiled in Tables 3 and 4.

No serum corticosterone and aldosterone levels were detected by radioimmunoassay 24 h after ADX, suggesting that most hormone binding sites in GR and MR are unoccupied. After administration of a single high dose of corticosterone (10 mg/kg, s.c.) to ADX rats, serum corticosterone levels were unphysiologically high for up to two hours (Table 3). After four hours, levels of corticosterone roughly mimicked the concentration of serum levels found at the diurnal peak or in highly stressed animals (Table 3, Sapolsky et al., 1986; Spencer et al., 1991), and probably still resulted in a full saturation and activation of intracellular GR and MR (Reul & de Kloet, 1985; Reul et al., 1987a,b). After 8 hours corticosterone levels had declined to serum levels as seen at nadir in normal and untreated rats (Table 3, Sapolsky et al., 1986; Spencer et al., 1991). Also four hours after administration of a single low dose of corticosterone (2 mg/kg, s.c.) to ADX rats serum corticosterone levels were raised to levels found at nadir, and may lead to a predominant MR but also some GR activation (Table 3, Reul & de Kloet, 1985; Sapolsky et al., 1986; Spencer et al., 1991; Reul et al., 1987a).

Two hours after administration of a single low dose of aldosterone (0.01 mg/kg, s.c.) to ADX rats, serum levels of aldosterone appeared to be similar to levels seen in untreated control or SHAM operated rats, which may lead mainly to MR activation alone (Table 4, Luttge et al., 1989; Loffreda et al., 1992; Reul et al.al., 1990, 2000). Four hours after giving a single high dose of aldosterone (0.5 mg/kg, s.c.) serum aldosterone levels were about 16 times higher than those in untreated control or SHAM operated rats (Table 4). Administration of the synthetic glucocorticoid agonist RU 28362 (4 mg/kg, s.c.) resulted in a maximal activation of GR alone with no detectable serum corticosterone and aldosterone levels.

Table 3. Summary of radioimmunoassays for blood serum corticosterone from different experiments.

treatment	corticosterone dose	time post injection	serum corticosterone levels (ng/ml)		
			I[a]	II[b]	III[c]
naïve	-	-	-	283 ± 48	-
SHAM	vehicle	4 h	-	225 ± 40	-
ADX	vehicle	0 - 24 h	n.d.	n.d.	n.d.
ADX	10 mg/kg	50 min	2545 ± 321	-	-
ADX	10 mg/kg	1.5 h	1682 ± 214	-	-
ADX	10 mg/kg	2 h	805 ± 143	-	-
ADX	2 mg/kg	4 h	-	50 ± 14	-
ADX	10 mg/kg	4 h	147 ± 27	261 ± 76	324 ± 73
ADX	10 mg/kg	8 h	29 ± 4	-	-
ADX	10 mg/kg	24 h	n.d.	-	-

[a] *papers IV, VI, VII,* [b] *papers II, III,* [c] injection of oligodeoxynucleotides into the dorsal hippocampus 2 h before corticosterone injection, *paper VI.*
Serum hormone levels were determined after a single s.c. injection of corticosterone or hormone vehicle (propylene glycol) after different time intervals to the time of killing in ADX rats. Data are expressed as mean values ± S.E.M.; n.d. < ≈5.7 ng corticosterone per ml blood serum = not detectable.

In the following, certain still unpublished observations will be described to further elucidate the feedback regulation of GR and MR in the acute ADX model. The effects of SHAM surgery, ADX and gluco- or mineralocorticoid administration on MR and GR mRNA levels have been analyzed in brain regions related to the regulation of the HPA axis and are summarized in Table 5. It appears that GR and MR are in most regions negatively regulated by their own ligands. However, in the anterior lobe of the pituitary their expression appears to be independent from this feedback regulation. MR expression seems to be autoregulated by MR activation alone in CA2 and CA3, and GR expression by GR activation in the hypothalamic paraventricular nucleus (PVN) and posterior lobe of the pituitary. In some cases, activation of both GR and MR can act synergistically (neocortex) or antagonistically (posterior lobe of the pituitary) on each other with regard to their own expression (Table 5). Thus, gluco- and mineralocorticoid regulation of GR and MR seems to be pronounced in the hippocampus with subfield specific variations, suggesting a complex regulation of hippocampal GR and MR expression by neuronal inputs. For example, both lesions of catecholaminergic and cholinergic input into the hippocampus increase the expression of GR and/or MR in the hippocampus (Yau et al., 1992; Herman, 1993).

Table 4. Summary of radioimmunoassays for blood serum aldosterone from different experiments.

treatment	aldosterone dose	time post injection	serum aldosterone levels (pg/ml)	
			I[a]	II[b]
naïve	-	-	391 ± 72	-
SHAM	vehicle	4 h	417 ± 84	-
ADX	vehicle	0 - 24 h	n.d.	n.d.
ADX	0.01 mg/kg	2 h	-	307 ± 47
ADX	0.01 mg/kg	4 h	-	n.d.
ADX	0.01 mg/kg	8 h	-	n.d.
ADX	0.01 mg/kg	24 h	-	n.d.
ADX	0.5 mg/kg	4 h	6277 ± 1019	-

[a] *paper II,* [b] *paper VII.*

Serum hormone levels were determined after a single s.c. injection of aldosterone or hormone vehicle (propylene glycol) after different time intervals to the time of killing in ADX rats. Data are expressed as means ± S.E.M.; n.d. < ≈ 16 pg aldosterone per ml blood serum = not detectable.

Table 5. Summary of the effects of surgery, adrenalectomy and adrenal steroids on MR and GR gene expression levels in different brain regions 4 hours after administration of the hormones in ADX rats.

m RNA and treatment	Neocortex	CA1	CA2	CA3	DG	PVN	LS	MS	PIT/ant	PIT/int	PIT/post
Effects of surgery											
MRmRNA											
SHAM + vehicle	↑	↔	↔	↔	↔	bdl	↔	↓↓	↔	↔	bdl
GR mRNA											
SHAM + vehicle	↔	↔	↔	↔	↔	↔	↔	bdl	↔	bdl	↔
Effects of ADX											
MRmRNA											
ADX + vehicle	↔	↑↑	↑↑	↑↑	↑	bdl	↑	↑↑	↔	↔	bdl
GR mRNA											
ADX + vehicle	↔	↑↑↑	↑↑↑	↑↑↑	↑	↔	↔	bdl	↔	bdl	↔
Effects of hormones											
MRmRNA											
ADX + ALDO	↔	↓↓	↓	↓	↓↓	bdl	↓	↔	↔	↔	bdl
ADX + CORT low	↔	↓↓	↓	↓	↓↓	bdl	↓	↔	↔	↔	bdl
ADX + CORT high	↓	↓↓	↓	↓↓	↓↓	bdl	↓↓	↓↓	↔	↔	bdl
ADX + RU 28362	↔	↓	↔	↔	↓	bdl	↓	↔	↔	↔	bdl
GR mRNA											
ADX + ALDO	↔	↓↓	↓↓	↓↓	↓↓	↔	(↓)	bdl	↔	bdl	↔
ADX + CORT low	↓↓	↓↓↓	↓↓↓	↓↓	↓↓	↓	↓	bdl	↔	bdl	↔
ADX + CORT high	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓	bdl	↔	bdl	(↓)
ADX + RU 28362	↓↓	↓↓↓	↓↓↓	↓↓	↓↓	↓↓	↓↓	bdl	↔	bdl	↓↓

Rats were s.c. injected with a single dose of either hormone (aldosterone, ALDO: 0.5 mg/kg, s.c.; corticosterone, CORT low: 2 mg/kg, s.c., CORT high: 10 mg/kg, s.c.; RU 28362: 4 mg/kg, s.c.) or hormone vehicle (propylene glycol). Arrows indicate significant changes in gene expression levels between SHAM + vehicle vs. control rat groups (effects of surgery), ADX + vehicle vs. SHAM + vehicle rat groups (effects of ADX) and ADX + hormone vs. ADX + vehicle rat groups (effects of adrenal steroid hormones). The statistical analysis have been performed by one-way ANOVA followed by Fisher's PLSD post-hoc test and Bonferroni's correction (Fisher's p-value multiplied by the number of brain regions analysed), n = 6 per animal group. ↑/↓: small increase/decrease, ↑ ↑/↓ ↓: moderate increase/decrease, ↑ ↑↑/↓↓ ↓: strong increase/decrease, (↓): tendency to decrease, ↔: unchanged mRNA levels, bdl: mRNA below detection limit. CA: Cornus Ammon areas, DG: dentate gyrus, PVN: paraventricular nucleus, LS: lateral septal nucleus, MS: medial septal nucleus, PIT/ant: anterior lobe of the pituitary, PIT/int: intermediate lobe of the pituitary, PIT/post: posterior lobe of the pituitary.

Fluorescence double-labeling immunohistochemistry demonstrates the existence of co-localization of GR-ir and GFAP-ir (yellow color) 1.5 hours after administration of a hormone vehicle in SHAM and ADX rats as well as in corticosterone injected ADX rats (Fig. 2). In surgically and injection stressed SHAM rats hormone ligand-occupied GR-ir (green color) is mainly located in the nucleus, but some unoccupied GR-ir is also found in the cytoplasm. After ADX, neuronal GR-ir is mainly found in the cytoplasm and most probably unoccupied by hormone ligands. After hormone administration the hormone binds to GR and the hormone-receptor complex is translocated to the nucleus of the nerve cell, where a strong GR-ir is found. ADX seems to increases the number of GFAP-ir astrocytes, which in addition are strongly labeled with nuclear GR-ir in all subregions of the dorsal hippocampus as compared to SHAM rats (Fig. 2). Administration of corticosterone does not seem to alter the number of GFAP-ir astrocytes with co-localized nuclear GR-ir as compared to ADX rats. This might be due to the early point of time after the hormone administration. An increase of number and intensity of GFAP-ir astrocytes in the hippocampus after ADX has been reported by many other investigators (O'Callaghan et al., 1989, 1991; Laping et al., 1991; Gould et al., 1992, Garcia-Segura et al., 1996), while corticosterone administration to ADX rats is suppose to lower GFAP-ir levels to values below those of SHAM controls (O'Callaghan et al., 1989, 1991; Laping et al., 1991; Garcia-Segura et al., 1996; Maurel et al., 2000). Thus, changes in the numbers of GR-ir astrocytes, after alteration in the pituitary-adrenal axis, underline a role also of the glial network in mediating the effects of GR on hippocampal plasticity, and astroglial in contrast to neuronal GR does not appear to undergo translocation after adrenalectomy.

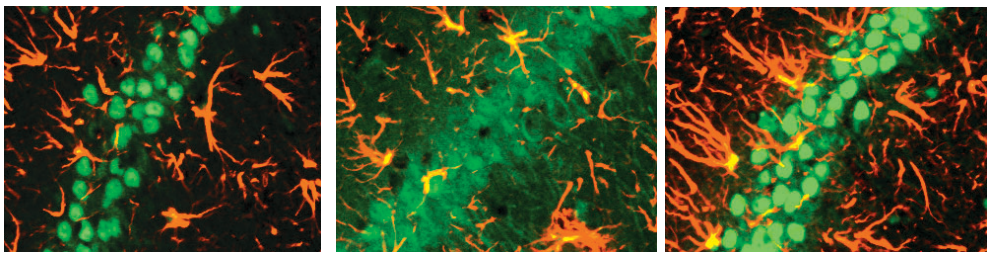

Figure 2
Analysis of GR-ir (FITC, green color) and GFAP-ir (Texas Red) by double immunofluorescence labeling in the CA1 region of the dorsal hippocampus of hormone-vehicle injected (s.c., 1.5 h) SHAM (left) and ADX (middle) rats and of corticosterone injected (10 mg/kg, s.c., 1.5 h) ADX rat (CORT, right). Photomicrographs showing a substantial co-localization of GR-ir and GFAP-ir (yellow color) in ADX and CORT rats. However, in the SHAM rat a lower degree of co-localization is observed. CA1, Cornus Ammon area. Scale bar = 20 µm, Bregma level = -3.5 to -4.5 mm.

Paper II describes the effects of gluco- and mineralocorticoid hormones on the local expression levels of bFGF, its high-affinity receptors FGF-R1 to -R3, BDNF and NT-3 in subregions of the dorsal hippocampus of ADX rats. The specific involvement of GR and/or MR was pharmacologically dissected by administration of either specific agonists or different hormone doses leading to activation of only the high-affinity receptor MR or the low-affinity receptor GR, or of both GR and MR together. The results are summarized in Tables 6 and 7. GR and MR activation causes a strong upregulation of bFGF mRNA levels throughout the whole hippocampus and a strong downregulation of BDNF mRNA levels with most prominent effects in the dentate gyrus (DG). NT-3 mRNA levels seem to be less affected by adrenal steroid hormones and were upregulated only in the DG after activation of both GR and MR. Notably, among the FGF receptor subtypes the FGF-R2 mRNA was selectively regulated by MR alone (see Table 6). Taken together, for a specific gene, GR/MR activation seems to drive transcription mostly in the same direction, either by up- or downregulation of mRNA levels. On the other hand, cell-specific factors, i.e. the cellular presence of the GR and/or MR and their interactions with each other and with a variety of transcription factors may determine the magnitude of the transcriptional regulation (Schüle et al., 1988, 1990; Strähle et al., 1988; Diamond et al., 1990; Pearce et al., 1994, 1998). GR and MR seem predominantly to act together in neurons (e.g. FGF-R1, BDNF and NT-3), whereas in non-neuronal cells the hormone effects can also be mediated by either of the receptors alone. The results clearly illustrate that the activation of GR/MR induces changes in neurotrophic factors and their receptors, which are unique for distinct cell populations in different subfields of the hippocampus. These concerted actions may influence plasticity of hippocampal neurons.

Table 6. Summary of GR and MR mediated neurotrophic responses to adrenal steroid hormones as studied on gene expression levels of neurotrophic factors in the dorsal hippocampus and the neocortex of ADX rats.

mRNA	CA1	CA2	CA3	DG	NC
bFGF	GR ↑↑↑	GR + MR ↑↑↑	GR + MR ↑↑↑↑	GR > MR ↑↑↑	GR ↑↑↑↑
FGF-R1	GR + MR ↓↓	n.e.	MR ↓	↔	bdl
FGF-R2	MR ↑↑	n.e.	MR ↑↑	MR ↑	GR + MR ↑↑
FGF-R3	↔	n.e.	GR + MR ↓↓	GR ↑	↔
BDNF	GR + MR ↓↓	n.e.	GR < MR ↓	GR > MR ↓↓↓↓	↔
NT-3	↔	↔	↔	GR + MR ↑	↔

Predominant glial expression is illustrated in grey shadow. Otherwise expression is predominantly in neurons. Arrows indicate significant changes in gene expression levels between adrenal steroid hormone and hormone vehicle treated ADX rats. The statistical analysis have been performed by one-way ANOVA followed by Fisher's PLSD post-hoc test and Bonferroni's correction (Fisher's p-value multiplied by the number of brain regions analysed), n = 6 per animal group. ↑: increase of gene expression, ↓: decrease of gene expression, ↔: no effect, ↑/↓: small effect, ↑↑/↓↓: moderate effect, ↑↑↑/↓↓↓: strong effect, ↑↑↑↑/↓↓↓↓: very strong effect, n.e.= not evaluated, bdl: mRNA below detection limit; DG = dentate gyrus; NC = neocortex.

Table 7. Effects of adrenalectomy and glucocorticoids as well as of stress on neurotrophic gene expression in the adult rat hippocampus. (Adapted from Schaaf et al., 2000)

animal surgery	treatment	time	*BDNF mRNA*			*NT-3 mRNA*			*bFGF mRNA*			Reference
			CA1	CA3	DG	CA1	CA3	DG	CA1	CA3	DG	
intact rats	immobilization stress	45 min	↓ (total hippocampus)									Nibuya et al., 1999
intact rats	immobilization stress	2 h	↔	↓/↔	↓	↔	n.s.	↔				Vaidya et al., 1999; Smith et al., 1995a
intact rats	immobilization stress	2 h	↔	↔	↔				↑ (total hippocampus)			Molteni et al., 2001; Vollmayr et al., 2001
intact rats	immobilization stress	2 h daily, 7 d	↓	↓	↓	↑	n.s.	↑				Smith et al., 1995a, 1995b; Butterweck et al., 2001
intact rats	immobilization stress	8 h	↓	↓	↓	↔	↔	↓				Ueyama et al., 1997
intact rats	unpredictable stress	daily, 10 d	↓ (total hippocampus)									Nibuya et al., 1999
intact rats	restraint stress	6 h daily, 21 d	↔	↔	↔	↔	↔	↔	↔	↔	↔	Kuroda & McEwen, 1998
intact rats	CORT (5 mg/kg, s.c.)	6 h							↑ (total hippocampus)			Molteni et al., 2001
intact rats	CORT (10 mg/kg, s.c.)	2 h	↔	↔	↓	↔	n.s.	↔				Smith et al., 1995a
intact rats	CORT (10 mg/kg, s.c.)	daily, 7 d	↔	↔	↓	↑	n.s.	↑				Smith et al., 1995a
intact rats	DEX (0.5 mg/kg, s.c.)	1-36 h							↑ (total hippocampus)			Mocchetti et al., 1996
intact rats	DEX (1 mg/kg, i.p.)	6 h							↑ (total hippocampus)			Riva et al., 1995
intact rats	DEX (5 mg/kg, s.c.)	daily, 4 d							n.s.	n.s.	↔	Woods et al., 1999
intact rats	DEX (5 mg/kg, i.p.)	2 - 48 h	↓ (total hippocampus)			↑ (total hippocampus)						Barbany & Persson, 1992
intact rats	DEX (10 mg/kg, i.p.)	6 h							↑ (total hippocampus)			Riva et al., 1995
ADX, 1d	hormone-vehicle, s.c.	4 h	↑	↔	↑	↔	↔	↓	↓	↓	↓	Hansson et al., 2000, *Paper II*
ADX, 3 d	saline, i.p.	5 h							↓ (total hippocampus)			Follesa & Mocchetti, 1993
ADX	hormone-vehicle, s.c.	daily, 3 d	↓ (total hippocampus)			↓ (total hippocampus)						Barbany & Persson, 1992
ADX	mock minipump	7 d	↑/↔	↑	↔	↔	↔	↔	↔	↔	↔	Chao et al., 1998
ADX	hormone-vehicle, s.c.	daily, 7 d	↔	↔	↔	↔	↔	↔	↔	↔	↔	Smith et al., 1995a Chao & McEwen, 1994
ADX, 7 d			↔	↔	↑							Lauterborn et al., 1998
ADX, 7 – 10 d			↔	↔	↔	n.s.	n.s.	↔				Lauterborn et al., 1995
ADX, 30 d			↔	↑	↑							Lauterborn et al., 1998
ADX	CORT (10 µg/hr)	7 d	↔	↓	↔	↔	↔	↔	↔	↔	↔	Chao et al., 1998
ADX, 3 d	CORT (30 µg/kg, s.c.)	3 - 24 h	↔	↔	↓							Schaaf et al., 1998
ADX , 3 d	CORT (300 µg/kg, s.c.)	3 -6 h	↓	↓	↓							Schaaf et al., 1997, 1999
ADX, 3 d	CORT (1 mg/kg, s.c.)	3 - 24 h	↓	↓/↔	↓							Schaaf et al., 1997, 1998
ADX, 1d	CORT (2 mg/kg, s.c.)	4 h	↓	↓	↓	↔	↔	↑	↑	↑	↑	Hansson et al., 2000, *Paper II*
ADX, 1 d	CORT (10 mg/kg, s.c.)	4 h	↓	↔	↓	↔	↔	↑	↑	↑	↑	Hansson et al., 2000, *Paper II*
ADX	CORT (40 mg/kg, s.c.)	daily, 7 d	↔	↓	↓	↔	↔	↓	↔	↔	↔	Chao & McEwen, 1994
ADX	immobilization stress	2 h daily, 7 d				n.s.	n.s.	↓				Smith et al., 1995b
ADX	immobilization stress + CORT(42.5 mg)	2 h daily, 7 d				n.s.	n.s.	↑				Smith et al., 1995b
ADX	DEX (1 mg/kg, i.p.)	daily, 3 d	↑ (total hippocampus)			↑ (total hippocampus)						Barbany & Persson, 1992

Abbreviations: (↑) increased, (↓) decreased or (↔) unchanged mRNA levels; DEX, dexamethasone; CORT, corticosterone; n.s., not shown.

However, in the above study, several questions regarding the mechanism underlying the GR/MR mediated changes in neurotrophic factor expression levels have not been addressed. Therefore, ***Paper III*** analyses the effects of adrenal steroids on the onset of bFGF transcription in glial cells, including observations in changes in number of bFGF expressing glial cells or changes in cell type specificity. To study bFGF expression in single, clearly distinguishable glial cells discrete subfields of the dorsal hippocampus of ADX rats, i.e. the stratum oriens and stratum radiata of the CA1 area and the molecular and polymorph layer of the DG, have been chosen. Activation of GR and MR seem to upregulate bFGF transcription levels in a subpopulation of glial cells and of scattered bFGF expressing neurons as assessed on autoradiographic emulsion coated microscopic slide preparations. Three classes of glial cells may be identified: The first class represents 20 to 30 % of glial cells where bFGF transcription levels seem to be independent of GR and MR activation. The second class representing 20 to 30 % of the glial cells can express bFGF transcripts after activation of GR and MR. The third class represents about half of the glial population and does not express bFGF transcripts at all under any of these conditions. ADX seems neither to affect the percentage of glial cells expressing bFGF transcripts nor the number of glial nuclear bFGF transcripts. The effects of ADX on bFGF expression may be caused by a reduction of cytoplasmic bFGF transcripts, since from one and the same section data were obtained by analysis of film autoradiograms. These show a strong downregulation of bFGF transcripts as seen after ADX. Thus, adrenal steroid depletion after ADX may have altered bFGF gene expression primarily post-transcriptionally rather than transcriptionally in accordance with several earlier observations (Murphy et al., 1990; Moffett et al., 1998; Touriol et al., 1999).

Paper IV investigates the corticosterone-induced downregulation of BDNF expression in the hippocampus. The rat BDNF gene promoter region is very complex consisting of four short 5' non-coding exons (exon I to exon IV) each of which are associated with a separate promoter. Exon V encodes the mature BDNF protein. The four different promoters give rise to four BDNF transcripts, each containing one of the 5'- untranslated exons in addition to exon V (Ohara et al., 1992, Timmusk et al., 1993). In addition, there are two different polyadenylation signals in the 3'- end of exon V, which leads to the generation of eight distinct BDNF transcripts (see Fig. 3). The four promoters are differentially expressed in various tissues and during development, and are also induced by different stimuli (Ohara et al., 1992; Timmusk et al., 1993, 1994a,b, Metsis et al., 1993; Bishop et al., 1994; Nakayama et al., 1994). We therefore studied the effects of corticosterone on the four different BDNF promoters. It seems

that in the hippocampus of ADX rats the promoter region II and especially the promoter region IV are involved in the GR/MR regulation of the BDNF gene. In line with the data of Schaaf et al. (1998) and Nitta et al. (1999) the time-dependent downregulation of hippocampal BDNF mRNA levels by corticosterone was closely followed by a decline in hippocampal BDNF protein levels. In our experiments, there was an initial rise in hippocampal BDNF protein levels, probably resulting from fast effects of corticosterone on neuronal excitability rather than from an action on gene expression via GR/MR (Joëls & de Kloet, 1994; Joëls, 2001). In addition, phosphorylation of the transcription factor CREB was increased by corticosterone in the DG, a region where GR/MR exert strongest effects on BDNF expression and thus, where an involvement of pCREB in the hormonal response can take place.

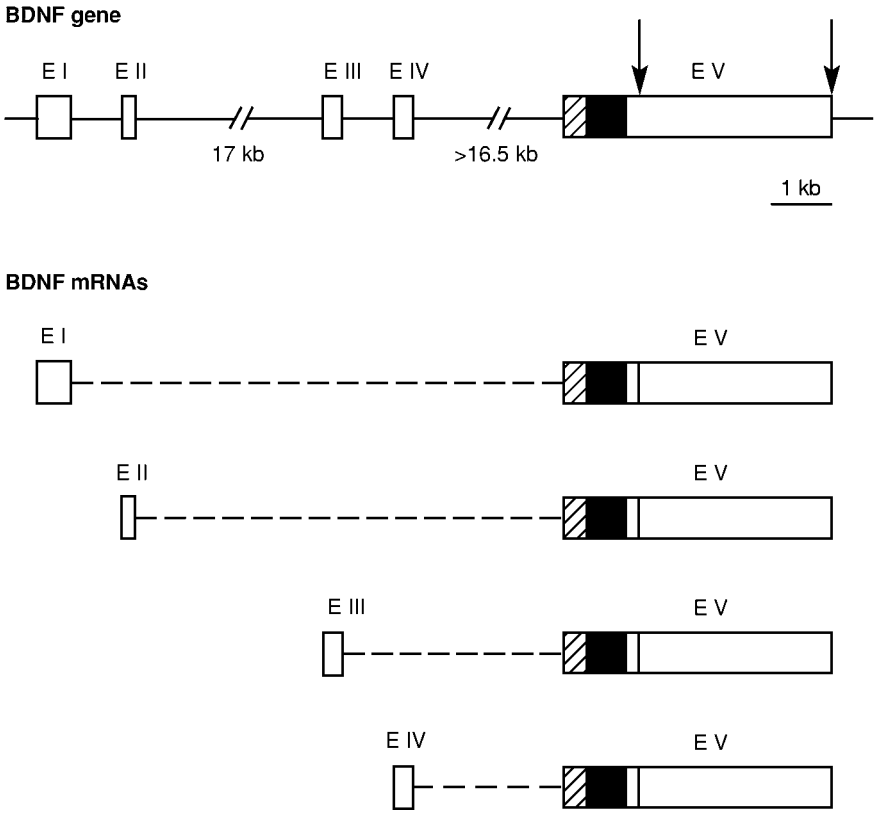

Figure 3
Schematic presentation of the rat gene and structures of BDNF mRNAs in relationship to the gene adapted from Timmusk et al., 1993. Exons are shown in boxes and introns as lines. Untranslational regions of the exons are indicated by open boxes, regions corresponding to the prepro-BDNF protein are indicated by hatched boxes, and regions coding for mature BDNF proteins are shown by black boxes. Arrows indicate two putative polyadenylation sites. The different exon-specific BDNF transcripts are shown below the gene with broken lines indicating the splicing out of the immature transcript.

Papers V and VI address the role of the inducible transcription factor *c-fos* in the regulation of neural activity and in the corticosterone-mediated regulation of neurotrophic factor expression. Among the number of rapidly induced genes, so called immediately early genes (IEGs) mediating the first stage of the genomic reaction, the transcription factor *c-fos* has obtained special attention because of its distinct spatiotemporal activation pattern upon a great variety of stimuli. *c-fos* forms highly active, heterodimeric transcription factor complexes called AP-1 with members of the jun-gene family. Thus, *c-fos* is involved in the regulation of a vast number of genes. Not surprisingly, with the rise of antisense oligodeoxynucleotide (ODN) technology (see below, Fig. 4) *c-fos* was one of the first genes selected to demonstrate that blocking the expression of a targeted gene in a region and time-specific manner is a powerful approach with which to study brain function. Our laboratory had a pioneering role in establishing this approach in brain research by demonstrating that *c-fos* antisense ODN not only blocked the central stimulants-induced expression of this gene, but also the expression of associated neurochemical behavioral signs, thereby suggesting a causal link between gene expression and behavioral performance (Dragunow et al., 1993; Heilig et al., 1993; Sommer et al., 1993). To date, a large number of investigators have used the antisense approach to study the function of *c-fos* via the behavioral effects elicited by suppression of this gene in various neural loci (reviewed by Sommer & Fuxe, 1997; Szklarczyk & Kaczmarek, 1997, 1999)

The method for inhibiting expression of a specific gene by antisense ODN was originally introduced by Stephenson and Zamecnik (1978). Antisense ODN are usually between 14 and 30 nucleotides long, consisting of either single-stranded DNA or DNA analogues with increased stability. They are complementary to a sequence within a target transcript and hence they are able to bind the target mRNA in a highly specific manner, thereby transiently inhibiting its protein synthesis (Fig. 4).

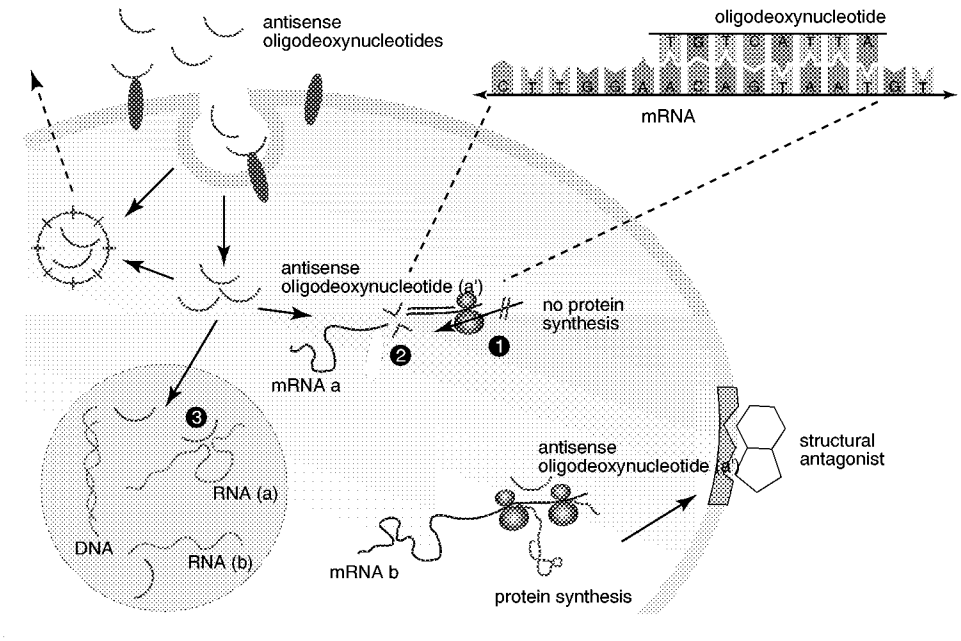

Figure 4
Proposed mechanism of action of the antisense oligodeoxynucleotide (ODN) technique. Antisense ODNs can be taken up into a cell by means o
f receptor-mediated endocytosis (upper left). Oligomers are then believed to Watson-Crick base-pair with their complementary mRNA-sequence ("mRNAa"). Other mRNAs lack this specific sequence, and are left unaffected ("mRNAb"). Blockade of protein synthesis is proposed to be achieved via several mechanisms of actions: 1. Steric blockade of the ribosome ("translational arrest"); 2. Enzymatic degradation of the RNA-component of the newly formed double helix (RNases); 3. Splicing blockade, that is, blockade of the formation of mature mRNA from the primary transcript. These mechanisms are believed to contribute to the effect of ODNs in various proportions in various cell types. The right part of the figure shows an example of a blockade gene product, in this case a receptor protein. The blockade achieved by administration of antisense ODNs is indistinguishable from that achieved following administration of a classical, stuctural antagonist. (Adapted from Sommer & Heilig, 1999).

In ***Paper V*** the principal methodology of the intracerebral administration of *c-fos* antisense ODN into a specific brain region, here the neostriatum, was worked out. To increase stability against nucleolytic activities most investigators used phosphorothioate ODN in which one of the oxygens in the internucleotide linkage is substituted with a sulfur atom (Stec et al., 1991). While this modification protects effectively against degradation, it increases binding of the ODN to proteins and thus contributes significantly to non-specific actions of the antisense ODN. In an attempt to reduce this potential problem we decreased the degree of the sulfur substitutions. Tissue penetration and intracellular uptake of these partially modified ODN were determined and could be correlated to the time course of the antisense effect. Of

particular interest was that the ODN were rapidly and efficiently taken up by the striatal neurons. Glial uptake appeared to be much weaker.

In view of the potential toxicity, the choice of relevant controls in antisense experiments is of great importance and several approaches have been applied. Originally, the corresponding sense strand was chosen. However, sense ODN may interfere with transcription rather than translation by binding to the genomic DNA. Scrambled ODN, i.e. randomized sequences with the same base composition as the antisense sequence, often have the problem of showing a different melting temperature than the antisense sequence. Mismatched sequences contain 1 to 4 bases that have been exchanged compared to the antisense sequence, and lead to reduced target binding, but sometimes they exhibit some degree of antisense action by themselves. Since each of these controls has their limitations, and in accordance with Stein (1996) we chose several different types of controls in our experiments.

Using highly sensitive RNase protection assays we found a low-level constitutive *c-fos* expression in the neostriatum of naïve rats. c-fos antisense treatment induced upregulation of several IEGs mRNAs, including junB, NGFI-A and c-fos itself. Since these genes all contain AP-1 binding sites in their promoters and are similar in their expression kinetics it was concluded that under physiological conditions c-fos, junB, and NGFI-A are negatively regulated by AP-1. The physiological relevance of a low-level *c-fos* expression for the activity of striatal neurons was demonstrated by studying the GABA release in the projection areas of the striatal neurons using a dual-probe microdialysis approach. Intrastriatally injected c-fos antisense ODN reduced GABA transmission in the striatonigral pathway but not in the striatopallidal pathway of freely moving rats, but by decreasing GABA levels in the substantia nigra. Thus, for a subset of striatal neurons a constitutive, low-level of *c-fos* expression, may facilitate GABA-ergic neurotransmission, and hence may increase their activity.

Paper VI shows the application of the above developed *c-fos* antisense approach for studying the corticosterone-mediated regulation of neurotrophic factor expression in the hippocampus. First, a time course experiment was performed to describe the effects of corticosterone administration (10 mg/kg, s.c.) in ADX rats on the hippocampal expression of the neurotrophic factors bFGF and BDNF, the hormone receptors GR and MR, and the IEGs *c-fos*, fosB, junB, c-jun and NGFI-A (Table 8). The peak hormone effect on the expression of bFGF, BDNF, GR and MR was found at four hours in most of hippocampal subregions. Furthermore, we found an early downregulation of all analyzed members of the *fos*-family expression levels, followed after a delay in time by a downregulation of junB expression

levels (Table 8). c-jun and NGFI-A expression levels were not affected by corticosterone. Expression of *c-fos* was less affected by corticosterone throughout the hippocampus, with the exception of an early negative regulation of *c-fos* mRNA levels in the DG region after 50 min. Earlier findings of corticosterone effects on *c-fos* expression reported conflicting results. In the brain, stress has been shown to induce *c-fos* mRNA levels and proteins (Senba et al., 1994; Cullinan et al., 1995; Senba & Ueyama, 1997; Herrera et al., 1997; Autelitano, 1998), but this effect does not appear to result directly from increases in adrenal steroids (Kononen et al., 1992; Hyder et al., 1994; Melia et al., 1994). Also, chronic treatment with the synthetic glucocorticoid dexamethasone has been shown to inhibit stress-induced *c-fos* expression in the PVN (Kovács and Sawchenko, 1996).

Using the same ADX animal model intrahippocampal injection of *c-fos* antisense ODN demonstrated that, exclusively within the CA1 region of the dorsal hippocampus, removal of the *c-fos* mechanism enhances the effects of activated GR/MR on bFGF and BDNF gene expression levels. The feedback regulation of GR and MR expression by corticosterone does not seem to involve a *c-fos* mechanism. A functional negative interaction between GR and Fos has been earlier described in tissue culture studies (Diamond et al., 1990; Jonat et al., 1990; Lucibello et al., 1990; Pearce and Yamamoto, 1993). Here, we demonstrate for the first time that the antagonistic *c-fos*/GR interaction seems to take place also *in vivo*. Within the pyramidal cell layer of the CA1 region there appears to exist only a small subpopulation of Fos-ir neurons, most of them also displaying GR-ir. It is therefore suggested that an antagonistic GR/c-Fos interaction in this small population of neurons could, via cell to cell interactions and thus network signaling, precipitate the appearance of a region-wide effect of the *c-fos* antisense treatment on bFGF and BDNF gene expression found in large numbers of glial and nerve cells all over the CA1 area.

Paper VII addresses aspects of the autoregulation of MR and GR expression after activation of MR alone or of both receptors in different brain regions of the ADX rat. It was found that activation of MR alone induced a biphasic autoregulation of MR expression levels in the medial septal nucleus (MS), in contrast to unchanged MR expression levels in the lateral septal nucleus (LS). In the hippocampus, activation of MR alone seems to negatively regulate GR and MR transcripts with peak responses at 8 h. After additional activation of GR the hippocampal peak time response of negatively regulated GR and MR was shifted to 4 h. Thus, dependent on the level of circulating hormones, the MS seems to be a region highly sensitive to MR-mediated effects of low-dose corticosterone and may take part in the control of limbic circuits, e.g. via the regulation of septo-hippocampal cholinergic pathways.

Table 8. Summary of the effects of corticosterone on immediate early gene expression levels in subregions of the dorsal hippocampus and the neocortex in ADX rats.

mRNA and time	neocortex	CA1	CA3	DG
c-fos mRNA				
50 min	↔	↔	↔	↓
2 h	↔	↔	↔	↓
4 h	↔	↔	↔	↔
8 h	↔	↔	↔	↔
24 h	↓	↔	↔	↔
fosB mRNA				
50 min	↔	↓	↓	↓
2 h	↔	↔	↔	↔
4 h	↔	↔	↔	↔
8 h	↔	↔	↔	↔
24 h	↔	↓	↔	↔
fra-1 mRNA				
50 min	bdl	bdl	bdl	↓
2 h	bdl	bdl	bdl	↔
4 h	bdl	bdl	bdl	↔
8 h	bdl	bdl	bdl	↔
24 h	bdl	bdl	bdl	↔
junB mRNA				
50 min	↑	↔	↔	↔
2 h	↔	↓	↓	↔
4 h	↔	↔	↑	↔
8 h	↔	↔	↔	↔
24 h	↔	↔	↔	↓
c-jun mRNA				
50 min	↔	↔	↔	↔
2 h	↔	↔	↔	↔
4 h	↔	↔	↔	↔
8 h	↔	↔	↔	↔
24 h	↔	↔	↔	↔
NGFI-A mRNA				
50 min	↔	↔	↔	↔
2 h	↔	↔	↔	↔
4 h	↔	↔	↔	↔
8 h	↔	↔	↔	↔
24 h	↔	↔	↔	↑

The statistical analysis was performed by two-way ANOVA (time*treatment) followed by Fisher's PLSD post-hoc test and Bonferroni's correction (Fisher's p-value multiplied by the number of brain regions analysed). Arrow shows significant changes between mRNA levels of corticosterone (10 mg/kg, s.c.) vs. vehicle treated ADX rats per time point. $p < 0.05$ was considered significant. ↑↓: small increase/decrease, ↔: unchanged mRNA levels, bdl: mRNA below detection limit, n = 5 per rat group. CA: Cornus Ammon area, DG: dentate gyrus.

CONCLUSIONS

In this thesis, evidence is presented that the adrenal steroid hormone mediated alterations in gene expression of several neurotrophic factors and receptors, in the hippocampus of ADX rats, are produced in a cellular and subregion specific manner, which appears to be unique for each analyzed gene. BDNF mRNA levels were negatively, and bFGF and NT-3 mRNA levels were positively, regulated by activation of both GR and MR with a peak effect 4 h after hormone treatment. Synergistic effects between activated GR and MR have been observed (e.g. for BDNF in DG) but do not seem to be as a common feature of the adrenocortical hormone actions on neurotrophic gene expression. Dependent on the region and the gene there was a regulation of gene expression due to activation of GR (bFGF in CA1) or MR alone (FGF-R2 in the whole hippocampus). Regions of increased sensitivity to gluco- and mineralocorticoid action seem to exist, which vary from gene to gene and seem to depend on the cell type.

We propose, based on the regional heterogeneity of the observed changes, that these complex interactions are not organized at the level of anatomically described divisions of the hippocampus, but instead are controlled in much smaller areas, so called trophic units. The concept of the trophic units was introduced by Agnati et al. (1995) and Fuxe et al. (1996b). A trophic unit is defined as being unique and consisting of small populations of neurons and glial cells (astrocytes, oligodendrocytes, microglia) together with blood vessels and extracellular matrix molecules, supporting each other's survival. A trophic unit may also have a unique responsiveness to GR and/or MR activation *inter alia* dependent on the GR and MR distribution pattern in relation to the trophic unit. These units are surrounded by and in communication with other units, which will help build up the glial/neuronal networks in the brain. Gluco- and mineralocorticoids may tune neurotrophism in neuronal/glial networks via a differential regulation of the activity of the trophic units, and in this way exert their effects on regional CNS homeostasis and plasticity. A change in the balance of GR and MR activity of a trophic unit will lead to reduced or increased trophism with consequences for nerve cell survival or neurogenesis. It also progressively creates a condition of disturbed neuroendocrine regulation and impaired adaptation (Fuxe et al., 1996b; de Kloet, 1998).

Using *c-fos* antisense ODNs it was demonstrated that within the CA1 region the inducible transcription factor *c-Fos* seems to counteract the effects of adrenal steroids on bFGF and BDNF gene expression. Based on the distribution of co-localisation between *c-Fos* and GR immunoreactivities it is concluded that the antisense effect is probably restricted to a small set

of *c-Fos*-ir/GR-ir neurons. These distinct neurons may, under normal conditions, increase the threshold for corticosterone action on bFGF and BDNF gene expression within surrounding neurons and glial cells. A trophic unit organization model would predict such network effects. Thus, within the CA1 region of the hippocampus a cascade of events could be initiated in scattered *c-fos*/GR-ir nerve cells leading to an altered output from these cells. This in turn may have consequences for transmitter and neurotrophic signaling in a large number of nerve and glial cells coordinated by extensive terminal networks of the *c-Fos*-ir/ GR-ir neuronal subpopulation. It may also represent a protective mechanism against an exaggerated regulation by GR of gene expression in the major neuronal/glial networks of CA1, which may have consequences for learning and memory as well as for the pathogenesis of stress-related disorders.

The present thesis also adds to the knowledge of the molecular mechanism of gene regulation of bFGF and BDNF. While there exist in fact some changes in the transcriptional activity of bFGF expression, the majority of the effects induced by adrenal steroid hormones in the hippocampus appear to be of a post-transcriptional nature. Furthermore, within the complex promoter of the BDNF gene, region II and especially region IV appear to be responsible for the down regulation of BDNF by adrenal steroid action.

The present studies on the feedback mechanism of adrenocortical hormone regulation dissected the effects of GR and MR on their own transcription. Activation of MR alone seems to regulate its own transcription in a highly region dependent manner. Positive (in MS), negative (in CA2) and no autoregulation (in LS) were found. The peak response of the MR mediated effect is at 8 h. By additional activation of GR the hippocampal peak time response of negatively regulated GR and MR was shifted to 4 h. The negative feedback on GR and MR expression was most pronounced in the hippocampus but also well developed in the septum. In the PVN and posterior lobe of the pituitary only GR contributed to the negative feedback.

Taken together, the impact of GR/MR mediated actions on BDNF and bFGF expression and other neurotrophic factors will probably have relevance for neurogenesis, neurodegeneration and psychotropic effects. The present thesis clarifies basic mechanisms underlying the therapeutic effects of drugs acting at glucocorticoid and mineralocorticoid receptors. This thesis will help define the role of brain GR and MR in neurotrophic responses and thus in brain plasticity. However, it remains to be determined whether the present non-physiological animal model (ADX) does in fact reflect adrenal steroid hormone signaling under normal physiological condition in terms of control of plasticity in the neuronal/glial networks.

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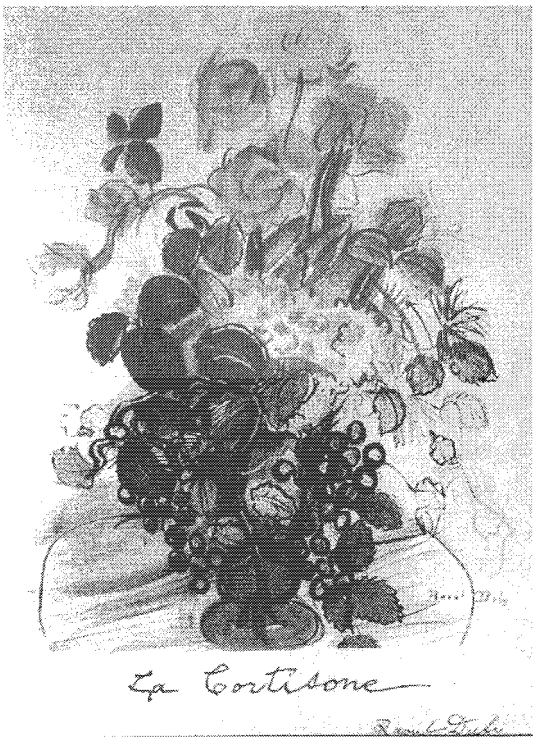

Figure 5
"La Cortisone" from Raoul Dufy.

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