CHAPTER - I

INTRODUCTION

One of the obvious advantages possessed by multicellular organisms is the ability to differentiate cells which can perform particular and disparate functions and thereby increase the versatility of the organism as a whole. However, the presence of a variety of functionally adapted cell types necessitates the development of efficient means of internal communication in order to coordinate and regulate many of their activities.

There are basically four ways in which one cell can influence the activity of another. Perheps one of the most common method by which neuronal cells communicate with other cells in distal parts of body is by means of directing nerve impulses with the help of nerves. In this communication system, the specificity of the message is determined by the way in which the ` wiring diagram' is laid down. Consequently it is sometimes called an `anatomically addressed system.'

The three remaining types of communications involve the release of chemicals and may be considered to be `chemically addressed systems'. The first, and simplest of these systems functions by virtue of close proximity : all cells affect their immediate neighbors non-specifically by consuming oxygen or metabolite from the interstitial fluid and releasing carbon dioxide and other products into it; such changes are incidental to general metabolism and probably serve no regulatory function. However, in second case, certain cells

influence their neighbors by the release of specific chemicals into the surroundings which have local effects restriced to cells within a very small radius - such effects are called `paracrine actions'.

The final type of intercellular communication is termed `endocrine' in which cells influence other cells by releasing into the circulating body fluid particular chemicals called hormones. Although the hormones come in to contact with every cell in the body, they only affect those target cells which possess the specific receptors for a particular hormone.

Among all these systems, the two main executive control systems are nervous and the endocrine systems; both appeared early in the evolutionary scale. Animal growth and development are among the most exciting processes in biology. If they are to proceed correctly, they must by regulated precisely by the neuro-endocrine orchestra. Role of thyroid-, sex- and growth hormone and adrenal glucocorticoids on neural ontogeny has been reviewed by Jacobson (1).

This capter reviews the literature concerning glucocorticoids. of the naturally occuring steroids, only corticosterone, cortisol, cortisone and 11 dehydro-corticosterone have appreciable glucocorticoid activity. Several synthetic compounds are known to possess glucocorticoid activity e.g. dexamethasone, methylprednisone,

triamcinolone etc (2).

SYNTHESIS OF GLUCOCORTICOIDS

Cortisol and corticosterone are the two glucocorticoid hormones produced by *zona fasciculata* of adrenal cortex. These glucocorticoid hormones are synthesized from cholesterol. Enzymatic hydrolysis of cholesterol esters gives rise to free cholesterol. This is one of the rate limiting steps in glucocorticoid biosynthesis and the rate of cholesterol release is controlled by adrenocorticotrophic hormaone (ACTH).

In mitochondria, free cholesterol is converted to s 5 pregnenolone by pregnenolone synthetase which cleaves the side chain at C18. This reaction is also thought to be rate limiting as the enzyme is susceptible to product inhibition; product inhibition could be overcome in the presence of ACTH by increasing the premeability of the mitochondrial membrane to pregnenolone. In smooth endoplasmic reticulum pregnenolone is converted to progesterone by Δ5 3ß - hydroxysteriod dehydrogenase, which is then hydroxylated either at C21 or C17. The C21 hydroxylated derivative (11-ß-deoxy-corticosterone) is finally hydroxylated at C11 in the mitochondria to corticosterone by action of enzyme 11-ß-hydroxylase. The 17α hydroxylation of progesterone in smooth

endoplasmic reticulum leads to production of cortisol by subsequent hydroxylations identical with those for the corticosterone. Thus the activity of the enzyme 17- α - hydroxylase determines the producaiton of two glucocorticoids secreted; this varies from species to species. Rats and mice lack the enzyme 17-α-hydroxylase and produce corticosterone almost exclusively. Whereas humans, primates, ruminants, cats and guinea-pigs secrete more cortisol than corticosterone (3).

CONTROL OF GLUCOCORTICOID SYNTHESIS

The glucocorticoid hormones are released in circulation as soon as they are synthesized and only trace amounts can be detected in adrenal gland. Thus the rate of secretion is determined by the rate of synthesis, which is controlled exclusively by ACTH. When ACTH binds to its membrane receptors, it causes rapid increase in glucocorticoid production. Binding of ACTH to receptors activates adenylate cyclase leading to production of cyclic AMP. Cyclic AMP then activates protein kinase, which in turn phosphorylates two proteins, one of which acts as a lipase and mobilizes cholesterol, while other promotes the conversion of cholesterol to pregenenolone (4,5). The secretion of ACTH is controlled by corticotropin releasing factor (CRF) which is synthesized in hypothalamus (6). CRF stimulates the secretion of ACTH from anterior pituitary via the hypophysial portal

system.

Glucocorticoids have negative feedback action on ACTH as well as CRF secretion. ACTH by itself also can reduce CRF secretion. CRF secretion can be increased directly by cholinergic neurones and indirectly by neurones releasing sereonin (5HT) (7). Noradrenaline or ϑ aminobutyric acid (GABA) releasing neurones can inhibit release of CRF.

High levels of corticosterone in the fetal stage inhibit the ACTH secretion in response to stress such as hypotension or hypoxemia (8). The ACTH secretion in the adrenalectomized adult rats was inhibited by dexamethasone implant at paraventricular nucleus (9). Feldman et al. (10) have shown that corticosterone implant in paraventricular nucleus inhibits ACTH and corticosterone responses and the release of CRF following neural stimuli in rats. Recently Makino et al. (11) have reported that glucocorticoids regulate CRF receptor mRNA levels in rat brain and pituitary. Both exogeneous corticosterone administration and endogenous corticosterone released during stress decrease CRF receptor mRNA levels in hypothalamic paraventricular nucleus and anterior pituitary.

CIRCULATING LEVELS OF GLUCOCORTICOIDS

In rats the principal glucocorticoid is corticosterone and plasma levels of corticosterone show diurnal fluctuation,

which is of neural origin and involves parallel fluctuation in ACTH and CRF release. The source of the circadian rhythm appears to be in the suprachiasmic nucleus of hypothalamus and is entrained to the light/ dark cycle. Rat being a nocturnal animal, the lowest plasma corticosterone levels are seen in early morning hours while peak levels are reported at the onset of darkness (12,13). Ahlersova et al.(14) have reported seasonal changes in circadian oscillations of serum corticosterone concentrations in rat in the course of the year. Marked differences in serum corticosterone levels were observed in different seasons.

Glucocorticoid levels in plasma also vary with the age of the animal. Before birth the level of corticosterone is high but falls immediately after birth and remains low till day 14 of postnatal life and after that it begins to increase and reaches the adult value (15,16).

Wide range of stress conditions such as heat, electric shock, surgery, cold stress etc. are known to elevate plasma corticosterone levels in rats. Depending on the stress, the increase ranged from 1.3 fold to 10 fold compared to the age-matched controls and the extent of increase was comparatively less in animals of age less than 15 days (16). Acute and chronic immobilization stress also produces large increase in plasma corticosterone levels in rats (11).

Circulating levels of glucocorticoids could also be affected by some other factors. Przegalinski et al.(17) have reported that adenosine and several of its analogues, dose-dependently increased plasma corticosterone levels in rats.

TRANSPORT AND METABOLISM OF GLUCOCORTIOIDS

In the circulation, about 90 % of the glucocorticoid hormones are present in the bound form and remaining 10 % are present in the free form. These hormones are bound mainly to corticosteroid binding globulin (CBG) and with less affinity to albumin in plasma. Hormone which is bound to plasma proteins is physiologically inert and protected from loss by renal filtration or metabolic degradation in the tissues. Corticosterone has a higher half life (50 to 90 minutes) than aldosterone (15 to 25 minutes) because under physiologic conditions about 90 % of the corticosterone is present in the bound form whereas in case of aldosterone the bound form represents about 60% of the total. The bound form of a hormone represents the metabolically inactive pool which can be converted rapidly to the free active form by dissociation from the binding proteins (3).

Inactivation of glucocorticoids occurs mainly in the liver by enzymatic reduction of Δ4-5 double bond and ketogenic oxygen substitution at the C3 position to form tetrahydro

derivatives of cortisol or corticosterone. These derivatives are conjugated with glucuronic acid to form water soluble metabolites, which can be readily excerted in the urine (7).

MOLECULAR MECHANISM OF GLUCOCORTICOID ACTION

To have better insights in glucocorticoid effects on target tissues it is important to have clear understanding of molecular mechanisms of action of these hormones. Glucocorticoids have intracellular receptors in target tissues, through which they can modulate expression of specific genes - a classical genomic action of glucocortoids. Besides, glucocorticoid hormones also have non-genomic actions which are mediated either by binding to specific membrane receptors or by accumulation of glucocorticoids in the biomembranes.

Genomic actions of glucocorticoids:

Being lipophilic in nature, glucocorticoids could easily gain entry into target cells by diffusion accross the plasma membrane. After entering into target cells, glucocorticoid hormones bind to their specific receptors present in cytosol. Upon binding of hormone, glucocorticoid receptor undergoes a conformational change, which enables the hormone - receptor complex to get translocated into nucleus. This hormone-receptor complex binds to specific acceptor sites of the DNA,

and thereby modulates the expression of target genes in a tissue-specific manner, resulting in a cascade of biological events (18-20).

Glucocorticoids can alter overall rate of RNA synthesis and also the processing of RNA. They can activate synthesis of specific messanger RNA (m RNA) by the transcriptional and post-transcriptional processes which regulate several enzymes of metabolic pathways in different tissues including brain (18-21).

The modulation of gene expression by glucocorticoids could be either by induction or repression mechanism. Many of the enzymes of metabolic pathways inducible by glucocorticoids (2,18,21). Glucocorticoids induce a protein named macrocortin (lipocortin) which inhibits phspholipid hydrolyzing enzyme phospholipase A_2; this is an example of inhibition of enzyme (22,23). Adrenalectomy leads to significant reduction of mRNA levels of transcortin (24). Similarly a plasminogen activator (serine protease) has also been reported to be inhibited by a inhibitory protein induced by glucocorticoids (25).

The glucocorticoid receptor belongs to superfamily of steroid nuclear receptors (26). Figure 1 shows structural and functional organization of steroid nuclear receptors. The glucocorrticoid receptor protein has been characterized and purified from different sources. It is a single polypeptide

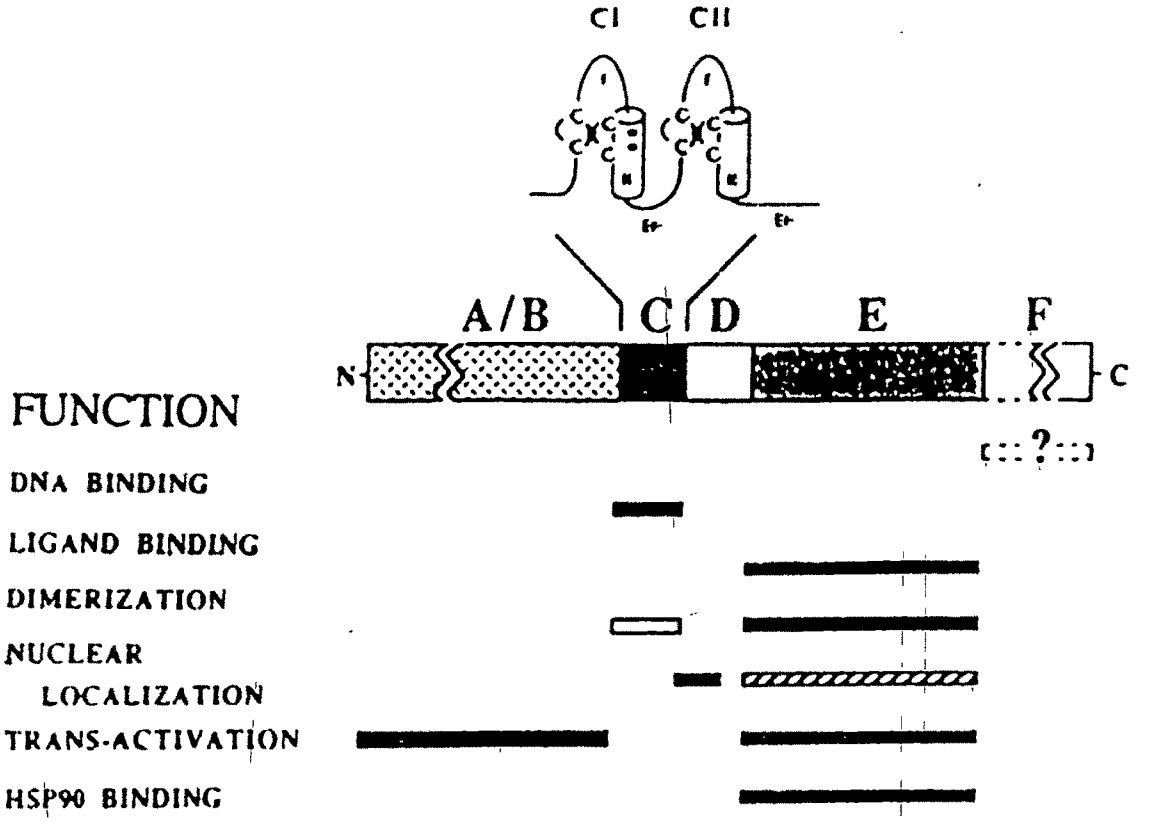

Figure 1

Structural and functional organization of steroid nuclear receptors.

with molecular weight 90 to 100 KDa(27). Proteolytic treatment shows that the receptor is composed of different functional domains (28).

The DNA binding domain is the best conserved among the members of the receptor superfamily. It consists of about 70 amino acids that fold into two zinc finger motifs. Each finger binds to a zinc ion that is tetrhedrally coordinated by conserved cysteines. The first finger (NH_2 - terminal) which determines response element specificity contains several hydrophobic amino acids apart from four cysteines. The second finger (COOH - terminal) consists of five cysteine and many basic amino acid residues, and is involved in protein - protein interactions such as receptor dimerization (29,30). The second best conserved domain of receptors is hormone binding domain, which binds to the ligand in hydrophobic pocket and participates in other functions such as nucleur translocation, receptor dimerization and transcriptional activation (29,31-33).

Glucocorticoid receptors also possess binding site for heat shock protein (hsp 90) that appears to modulate the subsequent response to hormonal signal (33). Heufelder et al. (34) have studied receptor medicated glucocorticoid effects on expression and synthesis of heat shock protein hsp-72 that is thought to play a role in thyroid autoimmunity. An additional independent transcriptional activation function is located

within NH_2- terminal of the receptor, which possesses a marked cell type and promotor specificity (35).

The function of glucocorticoid receptor in normal cells is regulated by a hormone and ATP dependent phosphorylation/ - desphosphorylation cycle which governs hormone binding (36,37) and transclocation of hormone-receptor complex to nuclei (38). Cyclic AMP decreased while cyclic GMP facilitated glucocorticoid binding to its receptors, and this binding is dependent on ATP and divalent cations (39). Phosphorylation of glucocorticoid receptors occurs at NH_2-terminal domain (40) by protein kinase A or proline directed serine kinase (39,41). Dephosphorylated form of glucocortiod receptor lacked the ability to bind to DNA and results into inactivation of the receptor (42). Protein kinase C activators and inhibitors are also known to affect functioning of glucocorticoid receptor (43-45). Danielsen et al. (46) have shown that phosphorylation of glucocorticoid receptor increase the binding of many transcriptional regulator proteins to DNA. Besides phosphorylation, other post-translational modifications such as glycosylation and acylation of glucocorticoid receptor can modulate receptor function indirectly by affecting the phosphorylation of receptors (47-49).

It has been shown by a various researchers that the fatty acids can modulate glucocorticoid receptor function (50-51). Polyunsaturated fatty acids have been shown to decrease

the binding of ^{3}H dexamethanasone to glucocorticoid receptors in rat liver. The inhition of binding is of mixed non-competitive type, suggesting that these fatty acids bind at a site on receptor different from the hormone binding site (52).

Recently Sato et al. (53) have reported down-regulation of glucocorticoid receptor gene expression and decreased number of glucocorticoid receptors by lipoprotein Lp (a) in human smooth muscle cells. However, low, very low and high density lipoprotiens has no effect on glucocorticoid receptors.

Radioligand binding studies have demonstrated that corticosteroids act through two types of receptors in brain. These receptors are referred to as type - 1 which is mineralocorticoid type (MR) in its binding properties and the type-2, which is identical with glucocorticoid receptor (GR) (54-59). This resolution into two central corticosteroid receptors systems is characterized by a difference in steroid specificity and neuroantomical distribution. MR binds the endogenous glucocorticoids of rat -corticosterone- as well as mineralocorticoid aldosterone with high affinity, and these receptors are widely distributed in kidney and other peripheral tissues. In brain, MR is predominently localized in septum and hippocampus (57, 58, 60-62). In constast, GR show high affinity for the potent synthetic analogs

dexamethasone and RU 28362 (58,63). These GR are widely distributed in the rat brain (58, 64-69) and throughout other tissues also. Spleen and thymus also contain GR in very high concentrations (70). In rat hippocampus both types of the receptors - MR and GR - are expressed (71).

Corticosteone binds to both MR and GR, but binding affinity to GR is 6-10 times lower than MR. At a very low dose of corticosterone (1 µg/100g body weight) 80% of GR gets occupied but for 95% occupation of GR a dose of 1 mg/100 g body weight is or corticosterone is required (58) Brain MRs bind cortisol with high affinity, but low capacity and are therefore largely occupied under basal conditions, whereas GRs are unoccupied under basal conditions because of low affinity, but become occupied during stress (72, 73). The differential occupation of these two receptors by corticosterone may be important for role of corticosterone in control of brain function during different physiological or pathological conditions (58,74).

In brain, levels of both MR and GR are regulated by glucocorticoid status. Adrenalectomy up-regulates while repeated stress down regulates GR in frontal cortex and amygdala (75-77). Spencer et al.(78) have reported that corticosterone down-regulates both the receptors MR and GR in brain regions, pituitary and immune tissue. In case of hippocampus, glucocorticoids autoregulate GR mRNA levels and

hormone binding sites in short term, but probably not in the longer term, whereas MR are little affected by glucocorticoids (72,79-81).

NON-GENOMIC ACTIONS OF GLUCOCORTICOIDS.

Any action of glucocorticoid harmones could be classified as non-genamic effect if it is of instantaneous onset or having a very short latency as well as rapid recovery following its removal. The effect should be insensitiveto inhibitors of RNA and protein synthesis. Veriety of steroid hormones including glucocorticoids are known to have several non-genomic effects on membrane structure and functions (82). Rapid effects of glucocorticoids on excitable membrane may be due to alterations in the characteristic of the membrane by intercalating into phospholipid bilayer. Accumulation of glucocorticoids within neuronal membranes can alter binding characteristics of neurotransmitters to their receptors and also the gating characteristics of ionic channels (83,84). In synaptic plasma membranes cortisol evokes an increase in Na^+,K^+ -ATPase activity (85).

Some of the glucocorticoid effects can be due to binding of glucocorticoids to specifc membrane receptors. The specific high affinity and low capacity glucocorticoid binding sits are present in kidney plasma membrane (86), hepatic plasma

membrane (87-89) and synaptic plasma membranes (90,91).

Glucocorticoids cause hyperpolarization of guinea pig ganglionic neuronal membranes under in vitro conditions in less then two minutes. This hyperpolarization was accompanied by change in the input resistance of the cells, indicating an involvement of ionic channels (92). Orchinik et al. (90). have reported presence of specific glucocorticoid receptors in synaptic plasma membranes of amphibian brain regions involved in regulation of behavior. Binding of corticosterone to these membrane receptors was linearly related to its potency of rapidly suppressing male reproductive behavior. They also suggested that similarly membrane receptors for glucocorticoids in spinal cord and peripheral tissues could be involved in stress-induced suppression of reproductive behavior. The specific high affinity binding sites for corticosterone are also present in brain mitochondria (90).

The glucocorticoids under in vitro conditions are known to alter oxidative metabolism of mitochondria from tissues such as liver, skeletal muscles and heart. These in vitro effects are purely non - genomic action of glucocorticoids, which includes inhibition of mitochondrial respiration and decreased oxidative phosphorylation or uncoupling and stimulation of mitochondrial ATPase (93-96). The glucocorticoid effects on mitochondrial oxidative energy metabolism are discussed in details in Chapter II.

GLUCOCORTICOIDS AND SECOND MESSENGER SYSTEMS

Glucocorticoids do affect the second messenger systems via modulating the effects of other hormones on second messengers. Mobely and Sulser (97) have shown role of glucocorticoids in regulating noradrenaline stimulated cyclic AMP production in the brain. Even in the peripheral tissues such as liver and adipose, glucocorticoids can alter the reponsiveness of adenylate cyclase to noradrenaline stimulation and hence production of cyclic AMP (98) Duman et al. (99) have shown that chronic administration of dexamethasone to rats enhances the sensitivity of cyclic AMP system in the brain to variety of agents known to directly simulate cyclic AMP production.

Saito et al.(100) have reported that G protein, a family of GTP-binding proteins that appear to play a central role in coupling hormonal/neurotransmitterreceptors to numerous intracellular effector systems, are also targets of glucocorticoids. In central nervous system, corticosterone differentially regulates the expression of GSa and Gia mRNA and protein levels in rat cerebral cortex, suggesting that some of the complex physiological and behavioral effects of this hormone on brain may be mediated at the level of G proteins. Glucocorticoids also alter calcium homeostasis within hippocampal neurones leading to increased calcium concentration and hyper-activation interrupting memory related

processes (101,102). Excitatory amino acids also stimulate intracellular calcium release; the action of these amino acid neurotransmitters are potentiated by glucocorticoids (103).

PHYSIOLOGICAL AND BEHAVLORAL EFFECTS OF GLUCOCORTICOLDS

Glucocorticoid hormones have numerous physiological and behavioral effects and play an important role in maintenance of various physiological processes and regulation of behavior.

Anti-inflammatory effects

Glucocorticoids are widely used as the anti-inflammatory agents because of their immunosupressive action. They inhibit inflammatory and allergic reactions in several ways. Glucocoticoids are known to stabilize lysosomal membranes and thereby inhibit release of lysosomal hydrolytic enzymes (82). The permeability of blood capillaries is decreased by glucocorticoids and thereby they could inhibit dipedesis of leucocytes and hence the number of circulating lymphocytes, eosinophils, monocytes and basophils are reduced. This is primarily due to decreased number of the cells in the circulation as a result of decreased dipedesis and redistribution of these cells from vascular compartment to lymphoid tissues; cellular lysis is not a mechanism for decreasing the number of these cells in circulation. The number of circulating neutrophils increased by glucocorticolds

due to accelerated release form bone marrow and reduced migration from the circulation (3,7). Glucocorticoids also decrease the humoral type immune responses by reducing the antibody production.

Many of the anti-inflammatory actions of the glucocorticoids appear to be related to their capacity to inhibit the release of arachidonic acid from lipids (104, 105). This inhibition has been demonstrated to be mediated through induction of phospholipase inhibitory proteins (lipocortins) by glucocorticoids (106). Duval (107) has reported that dexamethasone is able to inhibit the transformation of arachidonic acid into prostaglandins and also blocks its acylation into phospholipids in isolated mouse thymocytes.

Renal effects

Administration of glucocorticoids but not mineralocorticoids can restore glomerular filltration rate (GFR) and renal plasma flow to normal in adrenalectomized animals. Glucocorticoids facilitate free water excrection and uric acid excretion. The enzyme Na^+,K^+ - ATPase which plays an important role in sodium reabsorption and potassium secretion along the kidney tubules, has been shown to be highly dependent on glucocorticoid hormones (108,109). Adrenalectomy reduces the expression of $\alpha 1$ and not $\beta 1$ isoform mRNA of Na^+,K^+ - ATPase

in rat distal nephron (110) Assembly of α and ß subunits is required for functional maturation and proper insertion of Na^+,K^+ - ATPase into plasma membrane (111). A deficiency of adrenal glucocorticoids could lead to excess sodium retension and an inability to dispose off a water load and consequently increases susceptibility to water intoxication.

Gastric effects

Cortisol increcases gastric flow and secretion of hydrochloric acid, while it decreases the proliferation of gastric mucosal cells. These effects lead to peptic ulceration following chronic cortisol treatment (7).

Anti-growth effects

Large doses of cortisol are known to antagonize the effect of vitamin-D metabolites on calcium absortion from the gut, inhibit mitosis of fibroblasts and cause degradation of collagen. All of these effects lead to osteoporosis and reduction of fibroblast proliferation can cause delay in wound healing (3,7).

Chronic supraphysiological doses of glucocorticoids supresses growth harmone (GH) secretion and inhibit somatic growth. Martial et al. (112) have reported that glucocorticoids regulate mRNA levels of GH and pattern of GH secretion. Recently, veriety of glucocorticoid hormones are

shown to regulate mRNA and levels of growth hormone receptor protein and growth hormone binding protein in rat (113).

Although glucocorticoids increase the abillity of muscle to perform work, high doses lead to muscle atrophy and weakness. Glucocorticoids also exert pronounced effects on connective tissue, for which reason they are used clinically to inhibit fibrosis and for the treatment of various collagen diseases. Cortisol inhibits the synthesis of muco-polysaccharides and increases the degree of polymerization of hyaluronic acid, thereby substantially modifying the composition of the ground substance in connective tissue (3).

The effect of glucorcoticoid hormones on growth and development of the nervous system has been discussed separately in this Chapter.

Vascular effects

Pharmacological dose of cortisol enhances the pressor effect of norepinephrine on vascular smooth muscle. In absence of cortisol, the vasopressor action of catacholamines is diminished, and hypotension ensues. Thus glucocorticoids have an important role in the maintanence of normal arterial systemic blood pressure and volume though their support of vascular responsiveness to vasoactive substances (3,7). Cortisol is also known to enhance catacholamine synthesis by induction of enzyme phenylethanolamine N-methyltransferase

(PNMT) in adrenal medulla (114).

Effects on parturition

In sheep, a rapid increase in the rate of cortisol secretion by the fetal adrenal gland occurs at the end of gestation period and serves as initiation factor in parturition. Cortisol acts on the placenta by stimulating the conversion of progesterone to estrogen. The consequential decline in plasma progesterone and increase in estrogen induces a rise in prostaglandin $PGF_{2\alpha}$ which in turn causes contractions in maternal cotyledons and moymetrium. This prostaglandin besides having direct oxytoxic effect, also sensitizes myometrium to the action of oxytocin (3).

Even in humans glucocorticoids may have role in parturition. In cultures of human amnion cells, glucocorticoids stimulate PGE_2 synthesis (115, 116). It is possible that glucocorticoids have some physiologic relevence in regulating PGE_2 output by amnion cells during parturition (117).

Effects on behavior

Glucocorticoids are known to alter electrophysiological activity of neurones and hence affect mood, motivation and learned behavioral patterns (2,118). Most of the behavioral

studies have evaluated the effects of acute treatment on intact rats or replacement of glucocorticoids in adrenalectomized or hypophysectomized animals. High doses of glucocorticoids tend to antagonize experimentally-induced anmesia (119,120), to facilitate extinction of active avoidance (121,122), and to supress retention of passive avoidance (123). Micco et al. (124) have reported increased locomotor activity of adrenalectomized rats following corticosterone treatment. Long-term adrenalectomized rats have been shown to be less active in exploratory behaviour in open field; single dose of corticosterone could bring the reversal of this behavior (124). studies by Ehlers (125) has shown that long-term oral exposure to corticosterone does not have much effect on gross electrophysiological or spontaneous behaviour in rats. Orchinic et al. (90) have reported that corticosterone treatment of amphibians leads to rapid supression of male reproductive behavior and this effect was mediated by binding of corticosterone to specific receptors in synaptic plasma membrane in brain. Brain mitochondria also had specific high affinity binding sites for corticosterone (90).

The hippocampus plays an important role in memory, mood and behavior; all are affected by glucocorticoids although the associations are often complex (126). There is an 'inverted U shaped' relationship between glucocorticoid levels and hippocampal spatial memory (127,128). Low glucocorticoid

level or MR agonists potentiate memory related processes e.g. increasing long-term potentiation (LTP), the putative electrophysiological correlate of memory and reducing after hyperpolarization (AHP), which correlates negatively with spatial memory. Stress, high glucocorticoid levels and GR agonists reduce LTP and increase AHP, reducing neuronal excitability in hippocampus and attenuating memory (127, 129-131). Recently a direct correlation between hippocampal GR gene expression and spatial memory has been reported in aged rats (132).

METABOLIC EFFECTS OF GLUCOCORTICOIDS

Carbohydrate metabolism

Primary role of glucocorticoids in the control of corbohydrate metabolism is to maintain blood glucose levels and reserves of glycogen in liver and to a lesser extent in the heart and skeletal muscles. This is achieved by promoting gluconegenesis from amino acids and glycerol. Glucocorticoids have protein catabolic effects in extra-hepatic tissues especially in muscle, as a result of which amino acids released are mobilized to liver for synthesis of glucose and glycogen. Glucocorticoids inhibit glucose uptake in muscle and adipose tissue (3). Tanuka et al. (133) have reported that in leucocytes also the glucose uptake is inhibited by glucocorticoids.

In the liver, gluconeogenic enzymes such as glucose-6-phosphatase, Fructose 1,6-bisphosphatase and phosphoenol-pyruvate carboxykinase are induced by glucocorticoid treatment (3,7,134). Glucocorticoids promote lipolysis in adipose tissue as a result of which free fatty acids and glycerol are released; mobilized to liver. The glycerol is used as a substrate for gluconeogenesis whereas fatty acids and their metabolites inhibit enzymes of glycolysis i.e. glucokinase, phosphofructokinase and pyruvate kinase.

The glucocorticoid hormones in general stimulate gluconeogenesis in liver, inhibit the glycolysis and block the uptake of glucose by extra-hepatic peripheral tissues. Hence, glucocorticoid hormones exert an anti-insulin effect, which accounts for the phenomenon of glucose intolerance or eventual steroid or adrenal diabetes.

Glucocorticoids also block glucose transport in certain brain regions like hippocampus under both in vivo and in vitro conditions (135,136). Adrenalectomy results in an increase in local cerebral glucose uptake in rats(137). Horner et al.(138) have shown that dexamethasone causes translocation of glucose transporters form plasma memberanes to intracellular sites in cultured human fibroblasts. Therefore, glucocorticoids seem to decrease number of gulcose transporters in plasma membrane and therby decrease the glucose uptake.

Protein and amino acid metabolism

Glucocorticoids enhance the release of amino acids from proteins in skeletal muscles and other extra-hepatic tissues including the protein matrix of bone. Increased gluconeogensis by glucocorticoids from amino acids is associated with increased urea production via conversion of amino nitorgen to urea. Adrenalectomized rats showed a decrease in urinary nitrogen excretion, which was restored upon glucocorticoid treatment (139). Besides increasing protein breakdown in extrahepatic tissues, glucocorticoids also reduced amino acid uptake and protein synthesis in brain, muscle, lymphoid and other tissues (140-143). In muscle of rat treated with glucocorticoid, the ability of ribosomes to incorporate amino acids into protein was decreased (144). Yang and McElligot (145) have reported that corticosterone modulates adrenegic receptor, which in turn causes decreased protein synthesis and increased breakdown in skeletal muscle.

The amino acids taken up by liver are used not only to form glucose and glycogen but also to build new proteins (141). The protein anabolic effect in liver is an important exception to overall protein catabolic effects of glucocorticoids. Glucocorticoid treatment of rats enhances amino acid levels in liver (134,146) and induces the enzymes

involved in amino acid metabolism e.g. tyrosine transaminase and tryptophan pyrrolase (147, 148).

Lipid metabolism

Glucocorticoids exerts multitude of effects on metabolism of neutral lipids, phospholipids, fatty acids and cholestrol in a variety of tissues. Glucocorticoids are primarily lipolytic hormones and their lipolytic effect is in part due to potentiation of the lipolytic action of other hormones such as growth hormone, glucagon, catacholamines and thyroid hormone. In absence of glucocorticoids the lipolytic actions of these hormones are reduced to negligible proportions. This provides an example of numerous permissive actions of glucocorticoids hormones. In adipose tissue, the glucocorticoids cause increase lipolysis and falty acids released are mobilized to liver (3,7). In liver glucocorticoids increase triglyceride synthesis as judged by increasesd ^{3}H glycerol incorporation (149). The glucocorticoid mediated increased lipolysis in adipocytes is associated with decrease in lipoprotein lipase and increased hormone sensitive lipase gene expression (150). Glucocorticoids also indirectly stimulate lypolysis by blocking peripheral glucose uptake and utilization; by inhibiting this they block re-esterification of fatty acids into triglycerides in adipocytes. Chronic stress and exogenous glucocorticoid treatment leads to

increased fat deposition in mesentric areas of rat (151). This excessive fat deposition in specific areas of body reflects increased food intake rather than a change in the rate of lipid metabolism.

Glucocorticoids inhibit fatty acid and cholesterol synthesis in HeLa cells (152-155). Incorporation of fatty acids into lipids in human leukemia cell line is inhibited by glucocorticoids (156). In cultured human fiborblasts, hydrocortisone alone had no significant effect on ^{14}C-acetate incorporation into cholesterol and fatty acids. However, when used with insulin it had a marked stimulatory effect on incorporation of acetate into cholesterol and fatty acids and the activities of acetyl CoA carboxylase and fatty acid syntheatase (157). Lin and Snodgrass (158) have shown that dexamethasone increases 3 hydroxy 3 methyl glutaryl CoA (HMG CoA) reductase activity in cultured rat liver cells and liver from dexamethasone treated animals.

Melby et al. (159) have reported glucocorticoid-induce changes in lipid/phospholipids of rat liver microsomes. fibroblast cell line dexamethasone caused an increase sphingomyelin content by inducing the enzyme in biosythent pathway (160). In lungs, glucocorticoids are known to enhar synthesis of lecithin, which is a primary surfactant (16 Her et al. (162) have reported that glucocorticoid regula activity of phosphatidylinositol specific phospholipase

phosphorylation/dephosphorlation in basophilic leukemia cells. Kaur et al. (149) have reported effects of dexamethasone treatment on metabolism of neutral lipids and phospholipids in various rat tissues including liver, kidney, testes and heart. Bhargava et al. (163) have reported effects of in vivo corticosterone treatment on lipid metabolism in different brain regions of rat during development. Corticosterone treatment led to decrease in ^{14}C - glucose incorporation into cholesterol and phospholipids (163).

Glucocorticoids are known to increase sulfolipid synthesis in oligodendroglial cells (164-166). In rat hepatocytes, glucocorticoids up-regulate high affinity binding sites for high density lipoprotein (167).

BIOCHEMICAL EFFECTS OF GLUCOCORTICOIDS ON NERVOUS SYSTEM

Glucocorticoids appear to exert multitude of effects on the nervous system. These effects range from control of most basic processes of cellular growth and differentiation to alterations in electrophysiological activity, and finally to subtle yet important influences on mood, motivation and learned behavioral patterns. Although much progress has been made by neuroendocrinologists by working with simple systems such as cultured neuronal tumor cells or isolated avian retina, most of researchers have primarily focussed on the

rodent brain as target for glucocorticoid action (2).

Transport and distribution :

Transport of glucocorticoid from circulation into the brain extra-cellular spaces requires passage of the hormone across the blood brain barrier (BBB). Transport of glucocorticoids across BBB is non-saturable and therefore probably occurs via transmembrane diffusion. Corticosterone can cross the BBB and is transported to a considerably greater extent than cortisol, hydrococortisone or aldosterone (168). The factors that determine BBB permeability to different corticosteroids include lipid solubility, degree of hydrogen bonding in aqueous solution and interaction with binding protein. Interestingly, binding to plasma albumin does not seem to impede corticosteroid passage though BBB (169). Rapid dissociation from albumin apparently allows sufficient opportunity for the transport of the dissociated hormone. Brain glucocorticoid levels are ultimately decided not only by BBB permeability but also by the presence of intracellular binding sites to retain the hormone (170).

It has been shown by various workers that after injecting radiolabelled glucocorticoid to adrenalectomized rats, the label was found in all the brain regions examined (171,172). However, extent of retnetion of hormone varied among different brain regions. By autoradiographic studies it

has been shown that glucocorticoid retention was preferentially high in different areas of limbic system (55, 61,173-175), neocortex (173,176), cerebellum (177), olfactory nucleus (174), various motor nuclei of brainstem (178,179) and spinal cord (180).

In autoradiographic studies no labelling was found in the hypothalamus, but immunocytochemical studies with poly- and monoclonal antibodies have shown intense immunoreactivity in neurones of paraventricular nuclei, mediobasal hypothalamus, periventricular and preoptic areas of hypothalamus (181). Neuroglial cell labelling by glucocorticoid has essentially never been observed autordiographically in brain, optic nerve or peripheral nervous system (182, 183). This does not necessarily mean that glial cell are not targets for glucocorticoid because both astrocytes and oligodendrocytes are known to possess glucocorticoid receptors (184). Therefore, it should be made clear that depending on autoradiographic studies it is not always true that regions concentrating more glucocorticoid are more sensitive to these hormones than others. Regions like hypothalamus usually do not show any label autoradiographically but do possess glucocorticoid receptors and these receptors play an important role in glucocorticoid feedback on CRF secretion. Therefore, t concentrating ability of the regions may not be necessary fo

the physiological actions. The ability of liver to concentrate glucocorticoid is not surprising in the view of the fact that liver is one of the target of glucocorticoid action and it is the major site for metabolism and cojugation of glucocorticoid hormones into normal excretaory forms (185).

The subcellular distribution of labelled corticosterone has been studied in a variety of tissues including brain. In brain, the maximum label was found in cytosol (69%) than in nuclei (14%) and mitochondria (6.4%) as % of total activity in homogenates. Microsomes had lowest amount of lebelled corticosterone i.e. 4.6% (185). Butte et al. (186) have reported that myelin fraction of the rat brain also concentrates very high amount of lebelled corticosterone. Studies by Orchinik et al. (90) have shown that the specific binding of ^{3}H- corticosterone was most enriched in synaptic membranes and also in mitochondria but to a lesser extent.

Glucocorticoids and brain development

Glucocorticoids are known to exert a negative effect on brain growth and cell proliferation. Field (187,188) appears to have published the first reports that neonatal glucocorticoid administration to rats inhibits brain development. Later studies showed that this inhibition is manifested in several ways, the most general effect is a long-lasting decrease in cerebrum and cerbellar tissue weights in

rats (189-191). These decreases in brain weight are accompanied by significant reductions in DNA content suggesting that fewer cells are present in the brains of glucocorticoid treated animals. Biochemical studies showing decreased ornithine decarboxylase (192, 193) and thymidine incorporation into DNA (189, 190, 194, 196) indicate a general supression of cell proliferation with little effect of glucocorticoid treatment on cell loss (197). On the other hand, adrenalectomy results in inceased brain weight and generalized stimulation of somatic growth in animals. Biochemical analyses revealed significant increase in protein and DNA content and increased thymidine incorporation in various brain areas (2). Fetal dexamethasone pre-treatment decreases protein and DNA synthesis in neonatal rat brain as judged by ^{3}H- leucine incorporation into proteins and ^{3}H-thymidine incorporation into DNA (142).

Treatment with hydrocortisone to neonatal rats resulted in age-dependent temporary inhibition of cell proliferation in external granular layer of cerebellum and granule cell formation in dentate gyrus. After termination of treatment, a rebound in proliferative activity has occured but the recovery was not complete in case of cerebellum (198,199).

Because glial cell precursors are still actively dividing postnatally in the rat brain (200), one would expect

gliogenesis as well as neurogenesis to be influenced by neonatal glucocorticoid administration. Indeed,hydrocortisone-induced inhibition of glial cell proliferation has been observed in developing rat brain and optic nerve (201). Cessation of treatment was again followed closely by an increase in proliferative activity. Because astrocytes develop earlier than oligodendrocytes in the optic nerve, the major effect of glucocorticoid treatment was on the latter cell type. Thus depending on age of the animal and duration of glucocorticoid treatment, the formation of various cell populations in the nervous system can be suppressed by early glucocorticoid administration (201).

Glucocorticoids can alter brain growth in ways besides inhibiting cell proliferation. Studies have indicated that neonatal glucocorticoid administration to rats retards development of cortical dendritic spines (202,203) and reduce brain ganglioside levels (197,204,205). Because certain gangliosides are enriched in neuronal processes (206), both lines of evidence suggest that glucocorticoid may interfere with synapse formation. Gumbinas et al.(207) reported a long lasting reduction in myelination in brain after single injection with prednisone in 6-day-old rats. Bohn and Friedrich (201) also observed supression of myelination in optic nerve after hydrocortisone treatment to rats. Hydrocortisone is known to regulate expression of myelin basic

protein and proteolipid protein during brain development and it requires the presence of thyroid hormone for its action at post-transcriptional level (208).

Neonatal glucocorticoid administration also shows delayed maturation of sensory evoked potentials (209), swimming behavioral patterns (210) electroshock thresholds (211) and deficient avoidance conditioning (212) in rats. These findings indicate a massive interference of glucocorticoids with normal developmental process that is related, to neurochemical and neuroanatomical changes discussed above. The influence of glucocorticoid hormones on brain development does not represent particularly selective type of action, because several other tissues outside the nervous system are similarly affected (213). Studies have shown that glucocorticoids serve as a differentiating signal for various peripheral tissues (214).

Effects on differentiation and development of neurotransmitter systems

Neuronal differntiation at biochemical level is often assessed in terms of the neurotransmitter expression by a given cell population. Glucocorticoids are known to affect expression, development and metabolism of variety of neurotrasnmitter systems.

Glucocorticoid modulation of neurotransmitter expression is best exemplified by the effects of these hormones on catacholaminergic characteristics of cells derived from neural crest. Several cell types derived from embryonic structure called neural crest ultimately secrete one or more catacholamines (i.e. norepinephrine, epinephrine or dopamine) as neurotransmitter or hormones. There is substantial evidence indicating that nerve growth factor (NGF) and glucocorticoids are among the important humoral signals present in cellular microenvironment that are critical determinants of morphological and biochemical differentiation of these cell polpulations (215 - 217).

Glucocorticoids stimulate adrenergic differentiation in cultures of neural crest cells (218). In adrenal medulla the glucocorticoids cause induction of the enzyme PNMT, which is responsible for the formation of norepinephrine from epinephrine (219,220). Ciaranello et al.(221) have reported that hypophysectomy leads to a glucocorticoid reversible increase in proteolytic breakdown of PNMT. Apparantly glucocorticoids elevate adrenomudullary PNMT activity by increasing tissue S-adenosylmethionine (SAM) concentrations and thereby inhibiting PNMT degradation (222). SAM is a cofactor of this enzymes and also serves as methyl donor in several transmethylation reactions. Glucocorticoids play an important role in developmental increase in adrenomedullary

PNMT and the maintanance of adult levels of enzyme activities (114). Dexamethasone treatment over 6 to 13 days, elevates PNMT activity in hypothalamus and medulla of neonatal and adult rats (223).

Dunn et al. (224) reported that corticosterone treatment led to a selective increase in tyrosine hydroxylase (TH) activity in rat hypothalamus. Adrenalectomized rats show declined TH activity in median eminence which could be re-instated by dexamethasone administration (225). Although TH is generally considered as a rate limiting enzyme in the synthesis of all catacholamines, the enzyme that directly catalyzes the formation of norepinephrine is dopamine ß-hydroxylase (DBH). Like the other catacholamine synthesizing enzymes DBH is present in adrenal medulla, sympathetic ganglia and brain. As with PNMT and TH hypophysectomy leads to a gradual decline in adrenomedullary DBH activity in adult rats (226-228). The major effect of pituitary removal appears to be the increase in the rate of enzyme degradation; an effect reversed by administration of either ACTH or glucocorticoid (227,228). Ascorbic acid, the cofactor of DBH, markedly stabilizes the enzyme against proteolytic breakdown (229). Glucocorticoid hormones stimulate DBH activity in rat sympathetic ganglia (230). Adrenalectomy decreases significantly the activity of DBH in hypothalamus and brain

stem and administration of high dose of corticosterone to rats could increase basal activity of DBH only in hypothalamus (231).

Tryptophan hyroxylase (TPH) catlyzes the rate limiting step in the formation of sertonin (5HT). This enzyme (TPH) is a specific differentiation marker for serotonergic neurones in the nervous system. Glucocorticoid treatment leads to precoccious induction of TPH activity in neonatal rats (232,233). Adrenalectomy blocks the stimulation of TPH by reserpine or ethanol in mouse brain (234,235).

Development of choline acetyl transferase ChAT and acetylcholinestarase (AChE) is accelerated by glucocorticoids in embryonic chick cerebellum (236,237). The development of muscarinic receptors of acetylcholine can also be influenced by glucocorticoid treatment. Betamethasone treatment for four days to newborn mice showed an increased density of muscarinic receptors in several brain regions early in development but a decreased receptor density by 30 days of age (238). Using an electrophysiological approach, Puro (239) has reported interesting findings regarding the effects of glucocorticoids on development of cholinergic synapses in tissue culture. Dexamethasone exposure caused an accelerated maturation of cholinergic neurones in terms of their capacity for evoked neurotransmitter release.

Besides affecting the development and differntiation of neurotransmitter systems, glucocorticoids also influence neurotransmitter function in other ways. These include changes in turnover, precursor availability, re-uptake, receptor binding and receptor mediated effects. Glucocorticoid effects on such changes with respect to variety of neurotransmitters e.g catacholamines, serotonin, acetycholine, amino acids and neuropeptides in central nervous system have been reviewed by Meyer (2).

Regulation of glial cell differentiation

Whereas neuronal differntiation is partly accomplished by expression of various neurotransmitter synthesizing enzymes, glial cell differentiation can also be related to the presence of certain enzymes localized in specific glical cell types. The promotion of glial cell differentiation has been extensively studied as it relates to two glial enzymes glutamine synthetase (GS) in astrocytes and glycerol 3 phosphate dehydrogenase (GPDH) in oligodendrocytes.

The functions of GS in brain include ammonia detoxification and synthesis of storage form of glutamate for subsequent release and re-utilization by glutaminergic neurones. The effects of glucocordcoids on GS activity in mammalian neural tissues have been studied both *in vitro* and *in vivo*. Tissue culture work has shown that GS is

glucocorticoid inducible in mouse astrocytes primary culture (240,241), cultured rat hypothalamic cells (242), C_6 rat glioma cells (243, 244) and human retinoblastoma (245).

In vivo studies have dealt with the normal ontogeny and glucocorticoid responsivity of GS in rat brain. The specific activity of this enzyme increases throughout prenatal development (242) and then continues to rise postanatlly for differing periods in differnt areas of brain. Sensitivity of GS to glucocorticoid administration varied from region to region (247). In studies by Patel et al.(246), rats were given corticosterone for 3 days begining either on day 8,17,or 87. Significant increase in GS activity was observed in cerebellum at all the time points, whereas GS activity in olfactory bulb increased only in the youngest animals. Wu (247) reported that hydrocortisone administration to 15-day-old rats failed to alter GS activity.

The enzyme GPDH was the first enzyme to be indentified as glucocorticoid-inducible in the brain. It plays different role in different tissues; in muscles it maintains NAD^+ redox potential during anaerobic glycolysis, in liver it serves to provide glycerol 3 phosphate for lipid biosynthesis (248) and may also be involved in promoting gluconeogensis from glycerol. In case of brain, emphasis has been placed on a role of GPDH in synthesis of phospholipids for eventual

incorporation into myelin sheaths (249) but GPDH is not rate limiting with respect to myelin phospholipid biosynthesis (250).

The GPDH activity in rat brain is low at birth, begins to rise at postnatal day 10 to 15 and reaches adult value by day 40 (251). Northen blot analysis of developing rat brain revealed striking increase in GPDH trnscripts during the period (postnatal day 20 to 30) most associated with peak myelination (251,252). The normal developmental rise in GPDH activity could be inhibited by hypophysectomy and stimulated stimulated precocciously by hydrococortisone administration (251,253). Warringa et al.(166) have reported that in primary glial cell cultures hydrocortisone stimulates markedly the specific activity of GPDH and also the development of oligodendrocytes by directing bipotential progenitor cells to develop into oligodendrocytes. Besides, hydrocortisone also greatly enhanced the specific activity of 2'3' cyclic nucleotide 3' phophodiesterase (CNP diesterase) activity.

In addition to the role of glucocorticoids in brain development, they have also been implicated in ageing (254,255). Glucocorticoid treatment leads to irreversible hippocampal damage associated with neuronal cell death (256), and this could be mediated via activation of NMDA receptors (257,258) and due to cerebral energy depletion (259). Glucocorticoids inhibit neuronal glucose uptake (135,260), and

thereby interfere with energy supply to cells highly dependent on circulating stores. More importantly, glucocorticoids exacerbate neuronal damage caused by other agents including ischaemia, hypoxia, repeated seizures, antimetabolites and cholinergic neurotoxins (261,262).

Glucocorticoids are also known to reduce hippocampal neuronal dendritic length and branching (265) and impair neuronal capacity to recover from injury through inhibition of compensatory axo-dendritic sprouting (266). Glucocorticoids are known to reduce the synthesis and release of nerve growth factor (NGF) (262).

For the proper functioning and development of the central nervous system, high amount of energy is required in the form of ATP, which is furnished by mitochondria. The energy is required for maintainance of membrane potential, for active transport of solutes, for synthesis of neurotransmitters etc. Developing brain would require very high amount of energy for synthesis of variety of macromolecules such as DNA, RNA, proteins, lipids and polysaccharides and the neurones are very sensitive to disturbances in supply of energy sources. Many clinical conditions associated with disturbed functional behavior can be traced back to a deficient energy production (265). Furthermore, since nerve cells have a poor ability of regeneration, energy failure in the brain has far reaching

implications for the function and integrity of the organ and thereby for the survival of the organism as a whole.

From the foregoing, it is clear that neonatal glucocorticoid administration has deleterious effects on various aspects of brain development. Mainly the significant reduction in synthesis of macromolecules e.g. DNA, RNA proteins and lipids during development have serious consequences. Synthesis of these biomolecules is dependent on ATP hence it is very likely that glucocorticoids could be affecting the mitochondrial oxidative energy metabolism and thereby affect the brain development. Therefore the objective of this study was to examine the effects of corticosterone on mitochondrial function and structure-function relationship in the brain. Similar type of studies were also carried out on liver mitochondria as a model system.

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