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Synthetic Glucocorticoids Modulate Function of Neural Cells: Implications in Autoimmune Neurological Disorders

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1. Introduction

Glucocorticoids are hormones synthesized from cholesterol in the cortex of adrenal glands. Synthetic glucocorticoids are chemical derivatives synthesized from cholic acid obtained from cattle or steroid sapogenins. The chemical structure of these drugs is very similar to that of natural glucocorticoids. Therefore, the synthetic derivatives efficiently bind to intracellular receptors of glucocorticoid and mineralocorticoid, which promote a myriad of transcriptional and non-transcriptional processes. Synthetic glucocorticoids can trigger a cascade of events including neurotransmitter modulation, protein expression, neuronal firing or neurite growth. In addition, these substances are some of the most potent antiinflammatory and immunosuppressive agents available in human medicine with a good drug safety profile in humans. Thus, they are a valuable pharmacological tool for the treatment of acute and chronic neuroinflammation, and autoimmune disorders with neurological involvement. However, increasing evidence indicates that a high-dose or a long-term delivery of synthetic glucocorticoids may promote cognitive dysfunction, memory impairment, apoptosis, systemic hypersensitivity, urticaria-angioedema, neuronal degeneration, cerebral atrophy, major depression or steroid psychosis. Yet, these major side effects are relatively infrequent, the unrestricted use of glucocorticoids has to be avoided and systematic neuropsychological assessments are recommended to detect early neurological impairment. Herein, we discuss the mechanisms by which synthetic glucocorticoids may induce neural degeneration and other pathological changes in different brain regions. In addition, we describe the role of glucocorticoids in some autoimmune neurological disorders.

2. Glucocorticoids

The hypothalamus-pituitary-adrenal axis exerts an important regulation on neural functions mediated by the releasing of steroid molecules named corticosteroids. These hormones are synthesized from cholesterol in the cortex of adrenal glands (Fietta et al., 2009; Nicolaides et al., 2010). Two types of corticoids have been identified: glucocorticoids and mineralocorticoids. Glucocorticoids are produced in the inner region of the adrenal cortex (fascicular zone), while mineralocorticoids are synthesized in the outer part of the adrenal

cortex (glomerular zone) (Schimmer & George 1998). The name mineralocorticoid derives from early observations that associated these hormones with the homeostasis of sodium and water, whereas glucocorticoids obtained their name from initial observations that these steroids were involved in the metabolism of glucose. To date, it is well accepted that gluco- and mineralocorticoids have a number of pleiotropic and systemic effects (Figure 1) on cardiovascular system (Schimmer & George 1998; Ullian 1999), erythropoiesis (Amylon et al. 1986; King et al. 1988), calcium and bone metabolism (Thacker 2010), gastrointestinal tract (Black 1988), nitrogen excretion and glucose metabolism (Schimmer & George 1998), and exert a strong regulation in the immune system (Silverman et al. 2005). These physiological properties of glucocorticoids are useful in clinical medicine to treat and control a broad spectrum of diseases, such as: allergies, autoimmune diseases, cancer, hormonal replacement, asthma and sepsis. Nevertheless, glucocorticoids also have potentially harmful effects on several body systems, including the central nervous system. Some of these neurological impairments will be discussed below.

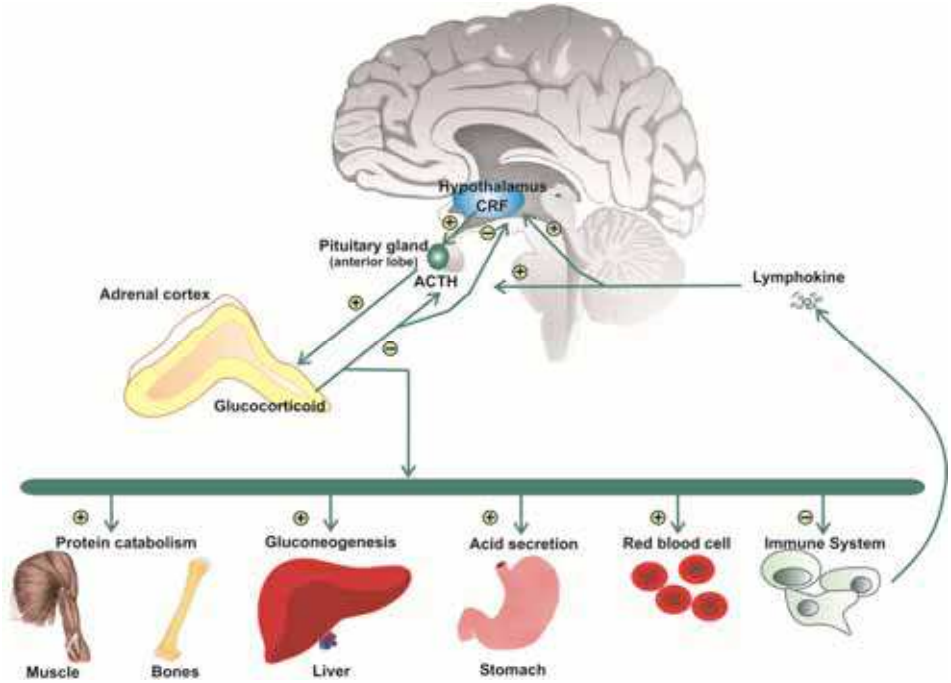

Fig. 1. Physiological effects of glucocorticoids and the hypothalamus-pituitary-adrenal axis. CRF = corticotropin-releasing factor ; ACTH = adrenocorticotrophin hormone; (+) indicates stimulation and (-) indicates inhibition.

3. Synthetic glucocorticoids

Synthetic glucocorticoids are usually synthesized from cholic acid obtained from cattle or steroid sapogenins found in plants. The chemical structure of these drugs is slightly different from that of natural glucocorticoids (Figure 2 A - B). For example, prednisolone

differs from cortisol only by a δ-1-dihydro configuration. Instead, bexamethasone and betamethasone have additional 9-α-fluoro and 16-β- or 16-α-methyl groups, respectively (Tegethoff et al. 2009).

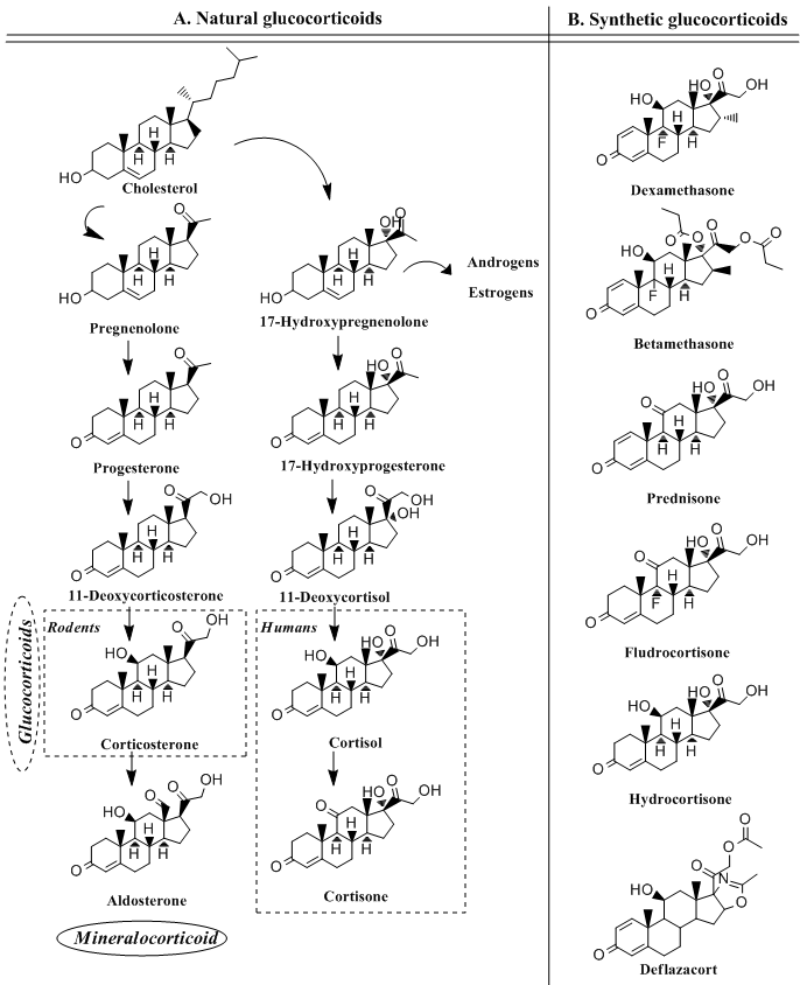

Fig. 2. Chemical structures of glucocorticoids. A. Metabolic pathways in the adrenocortical hormone biosynthesis. B. Synthetic glucocorticoids with anti-inflammatory and immunosuppressive activity.

Endogenous and synthetic glucocorticoids regulate a number of physiological and behavioural responses via intracellular receptors, which modulate the function of neural cells. In several brain regions, neural cells express two types of corticoid receptors: Type-1 receptors, also called mineralocorticoid receptors (MRs), and Type-2 receptors, also called glucocorticoid receptors (GRs) or NR3C1 (nuclear receptor subfamily 3, group C, member 1) (Fietta et al. 2009; Hoppmann et al. 2010; Marques et al. 2009; Prager et al. 2010). NR3C1

mediates the negative feedback in the HPA axis and in other limbic structures (de Kloet 2003; De Kloet et al. 1998). GRs have tenfold lesser affinity for corticosteroids than MRs (Table 1). The physiological outcome of these interactions is that GRs are mainly active during periods of abundant glucocorticoid secretion, such as circadian peak, systemic inflammation or stress. Thus, some of the functions of GRs include the regulation of energy metabolism, cellular homeostasis, stress-induced response, information storage and retrieval (de Kloet 2003; de Kloet et al. 1999; De Kloet et al. 1998). In contrast, MRs have a high affinity for corticosteroids; as a result, they are active when circulating glucocorticoid levels are relatively low. These receptors are highly expressed in hippocampus, septum, amygdala, frontal cortex, hypothalamic paraventricular nucleus and locus coeruleus (de Kloet 2003; De Kloet et al. 1998). One of the main functions of MRs is the regulation of basal HPA tone (de Kloet 2003; De Kloet et al. 1998).

Characteristics	**11β-HSD1**	**11β-HSD2**
Molecular mass	34 kDa	40 kDa
Activity (Km)	Low affinity Cortisol: 17 mM Corticosterone: 20 mM Cortisone: 200 mM	High affinity Cortisol:12 nM Corticosterone: 45 nM Dexamethasone: 140 nM
Inhibitors	Glycerhetinic acid Carbenoxolone	

Table 1. Glucocorticoid affinity in type-1 (11β-HSD1) and type-2 receptors (11β-HSD2). Modified from Buckingham 2006.

Glucocorticoid	**Plasma half-life**	**Potency**
Cortisol	**Short**	0.8
Cortisone	**$t_{1/2}$ 8-12 h**	1
Hydrocortisone		0.8
Deflazacort	**Intermediate**	5
Prednisone	**$t_{1/2}$ 12-36 h**	4
Prednisolone		4
Methylprednisolone		5
Triamcinolone		5
Dexamethasone	**Long**	25
Betamethasone	**$t_{1/2}$ 36–72 h**	30-40

Table 2. Potency and plasma half-life of natural and synthetic glucocorticoids commonly used in medicine.

The pharmacological effects of natural and synthetic glucocorticoids are mediated by the same genomic and non-genomic pathways (Buckingham 2006; Lowenberg et al. 2005; Lowenberg et al. 2006). The levels of efficacy, potency and pharmacological activity of synthetic hormones are determined by their pharmacokinetic properties (Table 2) (Fietta et al. 2009; Gonzalez-Perez et al. 2007). In clinic, synthetic glucocorticoids are commonly used as anti-inflammatory drugs for the treatment of allergies, rheumatic diseases, asthma, lymphoproliferative diseases and autoimmune disorders (Liberman et al. 2010). Most, if not all, of them can bind to both MRs and GRs, but with different affinities (Gonzalez-Perez et al. 2007). Remarkably, an increasing number of pre-clinical and clinical studies indicate that synthetic glucocorticoids can modify the citoarchitecture and function of glial cells, which alter the brain homeostasis.

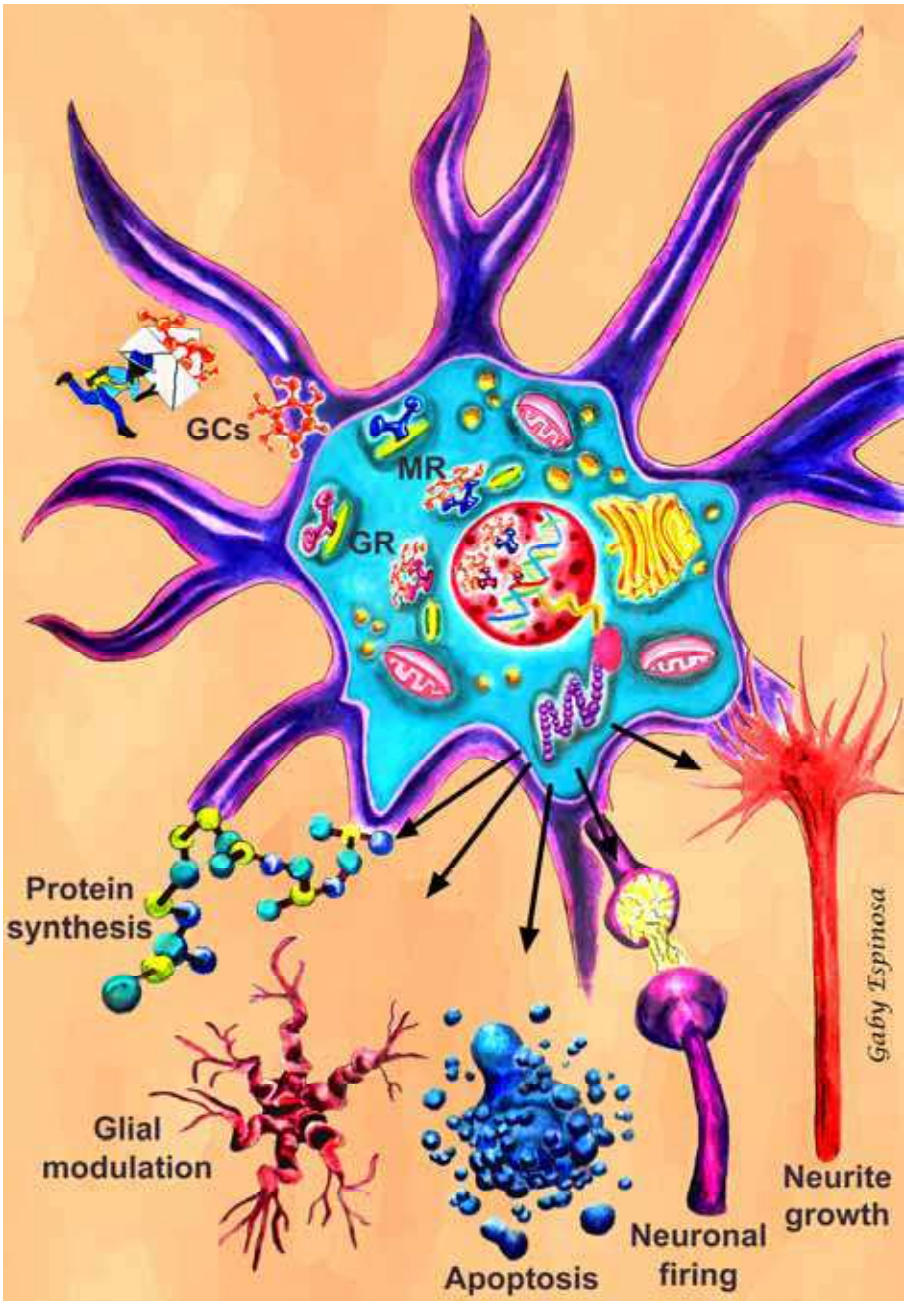

Fig. 3. Astrocytes modulate and/or promote several effects into the brain under the influence of glucocorticoids. Corticoids (GCs); glucocorticoid receptor (GR); mineralocorticoid receptor (MR).

4. Effects of synthetic glucocorticoids on astroglia

GRs and MRs are expressed not only by neurons, but also by glial cells or *neuroglia* (Bohn et al. 1991; Vielkind et al. 1990). Glial cells are non-neuronal cells that preserve neural homeostasis, form myelin, and provide support and protection for neurons. In fact, corticoids exert several effects into the brain by targeting glial cells that, in turn, modify the cerebral functioning (Figure 3). Astrocytes, collectively known as *astroglia*, are the most abundant glial cells and play multiple roles into the brain, such as: Neurotransmitter reuptake and release, modulation of synaptic transmission, nervous system repair, hormonal signalling, vascular tone regulation, preservation of blood–brain barrier and, in some cases, astrocytes may function as neural stem cells (Gonzalez-Perez & Alvarez-Buylla 2011; Kettenmann & Ransom 2005).

Astroglia expresses the intermediate filament glial fibrilliary acidic protein (GFAP), which is used as cellular marker of these cells (Ihrie & Alvarez-Buylla 2008). Interestingly, astrocytes contain high number of GRs and MRs; consequently, astrocyte function and their GFAP expression are highly susceptible to glucocorticoids (Lambert et al. 2000; Rozovsky et al. 1995). Some of the effects of glucocorticoids on gene and protein expression in astrocytes are summarized in the table 3.

Protein / gene	Function	Glucocorticoid effect	Reference
Glial fibrilliary acidic protein (GFAP)	Intermediate filament protein	Upregulation	(O'Callaghan et al. 1991; Ramos-Remus et al. 2002)
Glial glutamate transporter (GLT-1)	Neurotransmitter recycling	Upregulation	(Reagan et al. 2004; Zschocke et al. 2005)
Glutamine synthetase	Neurotransmitter recycling	Upregulation	(Hansson 1989; Vardimon et al. 1999)
Basic fibroblast growth factor (bFGF)	Neurotrophic protein	Upregulation	(Niu et al. 1997)
S100β	Ca2+-binding neurotrophic protein	Upregulation	(Van den Hove et al. 2006)
N-myc downstream-regulated gene (Ndrg2)	Cell differentiation	Upregulation	(Nichols et al. 2005)
Lipocortin-1	Anti-inflammatory protein	Upregulation	(McLeod & Bolton 1995)
Nerve growth factor (NGF)	Neurotrophic protein	Downregulation	(Niu et al. 1997)
Vimentin	Intermediate filament	Downregulation	(Avola et al. 2004)

Table 3. Effects of glucocorticoids on protein and gene expression in astrocytes.

In vitro administration of dexamethasone, corticosterone or aldosterone inhibits astrocyte proliferation in a dose-dependent manner (Crossin et al. 1997). This effect seems to be mediated by neural cell adhesion molecules, which inhibit activation of mitogen-activated protein (MAP) kinase (Krushel et al. 1998). The corticoid-induced inhibition of cell

proliferation and growth retardation may also be enhanced by a concomitant reduction in the production of insulin-like growth factor 1 (IGF-1) in parenchymal astrocytes (Adamo et al. 1988). On the other hand, the overexpression of GFAP and chondroitin sulfate proteoglycans in reactive astrocytes has been related to a deficient neuronal repair and less neurite outgrowth. Methylprednisolone can revert these adverse effects by downregulating astrocyte activation (Liu et al. 2008) and reducing the number of GFAP-expressing astroglia (Sabolek et al. 2006). Further studies indicate that dexamethasone can modify hippocampal neuron development and survival by decreasing the mRNA levels of nerve growth factor (NGF) (Niu et al. 1997) and GFAP in hippocampus and neocortex (Aleong et al. 2003). In contrast, other reports using corticosterone (Bridges et al. 2008), prednisone (Ramos-Remus et al. 2002) and deflazacort (Gonzalez-Castaneda et al. 2007) reported an increase in the number and cytoplasmic processes of hippocampal and cortical astrocytes. The reason for these discrepancies is not well-known, but they appear to be mediated by dose- and region-dependent phenomena (Gonzalez-Perez et al. 2001).

Glucocorticoids not only modify the function of glial cells in adult stages, but also during prenatal development. Prenatal betamethasone administration delays both astrocyte and capillary tight junction maturation (Huang et al. 2001a), as well as the myelination in the corpus callosum (Huang et al. 2001b). Remarkably, glucocorticoid effects are not limited to the modulation of cell morphology or molecular expression in neuroglia. Instead, they are key modulators of glycogen metabolism and neurotransmitter transporter homeostasis as demonstrated in several experimental models. For instance, cortical astrocytes exposed to dexamethasone show a reduction of noradrenaline-induced glycogen synthesis (Allaman et al. 2004). Prednisolone, betamethasone and dexamethasone inhibit the transporter uptake of monoamines producing effects on physiological and behavioral processes (Hill et al. 2010). The glial glutamate transporter-1 (GLT-1) is also affected by synthetic glucocorticoids. In cortical astrocytes, dexamethasone provokes a marked increase in the GLT-1 transcription and GLT-1 protein levels (Zschocke et al. 2005). GABAergic neurons are also affected by synthetic glucocorticoids that impair their rhythmic firing, which may lead to cognitive deficit (Hu et al. 2010). Taken together, this evidence indicates that synthetic glucocorticoids exert a strong modulation on neural cells by modifying protein expression, neurite growth, cell proliferation, neurotransmitter uptake, neuronal firing, vasculature function and neuronal degeneration.

4.1 Implications in autoimmune neurological disorders. Pathological features observed in patients upon GCs administration

One major application of synthetic glucocorticoids is the treatment of acute and chronic neuroinflammatory disorders, such as multiple sclerosis, autoimmune encephalomyelitis, immune rejection, Parkinson's disease, retinal degeneration and others. Increasing evidence indicates that the therapeutic efficacy of glucocorticoids against autoimmune disorders may rely not only on their well-known anti-inflammatory effects, but also on their properties of neuro-gliomodulation (Gonzalez-Perez et al. 2007). For instance, methylprednisolone has a synergistic effect with Nogo-66 receptor protein, which promotes functional recovery and axonal growth in a model of spinal cord contusion (Ji et al. 2005). Methylprednisolone also mediates anti-apoptotic effects on oligodendrocytes by activating STAT5 proteins, which up-regulate a splicing isoform of the bcl-x gene (Xu et al. 2009). On the other hand, prednisone contributes to attenuate experimental autoimmune encephalomyelitis by preventing the reduction of brain-derived neurotrophic factor (BDNF) and NGF mRNA

expression into the brain (Chen et al. 2009). Promising results have also been obtained with dexamethasone and fluocinolone in several studies, i.e. dexamethasone reduces astroglial reactivity to implanted neuroprosthetic devices in rat cortex (Spataro et al. 2005), whereas intravitreous administration of fluocinolone attenuates retinal degeneration (Glybina et al. 2010). Further evidence suggests that dexamethasone produces immunosuppressive effects on the astrocyte response to interleukin-1-beta stimulation (Pousset et al. 1999) and counteracts blood–brain barrier failure by decreasing transendothelial permeability (Cucullo et al. 2004).

Despite synthetic glucocorticoids have demonstrated an adequate safety profile, increasing clinical experience and experimental studies indicate that corticoids are able to promote cognitive dysfunction, anxiety, cerebral atrophy, depression and steroid psychosis. One of the first studies that associated the glucocorticoid delivery with mood disorders in humans was reported in prednisone-treated asthmatic children (Bender et al. 1991). However, adults are also affected by corticoids as demonstrated in healthy volunteers that, after receiving a high-dose prednisone or dexamethasone, showed mood changes and memory impairment (Keenan et al. 1996; Schmidt et al. 1999; Wolkowitz 1994). Cerebral atrophy was reported after a long-term treatment with glucocorticoids in patients with no previous history of central nervous system affection (Bentson et al. 1978; Hara et al. 1981). Other immunologic disorders, such as systemic corticosteroid hypersensitivity (de Sousa et al. 2010; Rachid et al. 2011), toxic epidermal necrolysis (Navarro Llanos et al. 1996) or urticaria-angioedema (Gomez et al. 2002), have also been associated with the administration of glucocorticoids.

Under specific circumstances synthetic corticoids may impair or even potentiate the progress of neurological disorders as reported in experimental models of Alzheimer's disease, hypoxia or prenatal glucocorticoid delivery. This fact appears to be particularly important in neurodegenerative disorders related to oxysterol production such as Alzheimer's disease and multiple sclerosis. Oxysterols are oxidized forms of cholesterol that provokes oligodendrocyte apoptosis. Dexamethasone exacerbates the apoptotic effects of oxysterols on oligodendrocytes, resulting in secondary necrosis (Trousson et al. 2009). Cerebral vasculature is also altered by exposure to dexamethasone that may deteriorate hippocampal functions (Neigh et al. 2010). In hypoxia models, dexamethasone increases the expression of Bnip3, a pro-apoptotic Bcl-2 family, which impairs hypoxic tissue damage (Sandau & Handa 2007).

Neuronal function and survival are also affected by synthetic corticoids. Dexamethasone increases oxidative stress and expression of monoamine oxidase A and B, resulting in a higher loss of dopaminergic neurons (Arguelles et al. 2010). Oral administration of prednisone or deflazacort promotes neuronal degeneration of pyramidal neurons in CA1 and CA3 hippocampal regions (Gonzalez-Castaneda et al. 2007; Gonzalez-Perez et al. 2007; Ramos-Remus et al. 2002). Dexamethasone also decreases the number of neurons in the striatum (dorsomedial caudate-putamen) and hippocampus (dentate gyrus, CA1 and CA3 subfields), which may account for some of the cognitive deficits seen following administration of glucocorticoids to healthy volunteers (Haynes et al. 2001). Glucocorticoids also target the developing brain as reported in children exposed to synthetic glucocorticoids *in uterus*, who showed a reduction in fetal and, in some cases, newborn and infant HPA axis activity (Tegethoff et al. 2009). Other studies indicate that prenatal dexa- or betamethasone exposure also affects postnatal cognitive functions (Hauser et al. 2007; Hauser et al. 2006), reduces the survival of cholinergic neurons (Emgard et al. 2007), and produces permanent changes in the cytoarchitecture within midbrain dopamine nuclei (McArthur et al. 2005).

Taken together, this evidence indicates that synthetic glucocorticoid may have detrimental effects on glial and neuronal integrity. Therefore, some authors have proposed that uncontrolled use of glucocorticoids may predispose to the development of a range of psychiatric and neurological conditions throughout life.

5. Conclusion

Synthetic glucocorticoids are a valuable therapeutic strategy against neuroinflammation and autoimmune disorders with neurological involvement. In fact, anti-inflammatory strategies receive growing attention for their potential to prevent pathological deterioration in multiple sclerosis (the most prevalent chronic autoimmune disease of the central nervous system), Parkinson's disease, autoimmune encephalomyelitis and other severe neurological disorders. Nevertheless, the uncontrolled use of glucocorticoids must be avoided because of their deleterious potential on cognition, neuronal survival and apoptosis induction. Yet, in those clinical situations where glucocorticoid use is necessary, a continuous neuropsychological assessment is strongly recommended to detect a possible neurological deterioration.

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7. References

Adamo, M., Werner, H., Farnsworth, W., et al. (1988). Dexamethasone reduces steady state insulin-like growth factor I messenger ribonucleic acid levels in rat neuronal and glial cells in primary culture. *Endocrinology*, Vol.123, No.5, Nov 1988, pp. (2565-70).

Aleong, R., Aumont, N., Dea, D., et al. (2003). Non-steroidal anti-inflammatory drugs mediate increased in vitro glial expression of apolipoprotein E protein. *Eur J Neurosci*, Vol.18, No.6, Sep 2003, pp. (1428-38).

Allaman, I., Pellerin, L., & Magistretti, P.J. (2004). Glucocorticoids modulate neurotransmitter-induced glycogen metabolism in cultured cortical astrocytes. *J Neurochem*, Vol.88, No.4, Feb 2004, pp. (900-8).

Amylon, M.D., Perrine, S.P., & Glader, B.E. (1986). Prednisone stimulation of erythropoiesis in leukemic children during remission. *Am J Hematol*, Vol.23, No.2, Oct 1986, pp. (179-81).

Arguelles, S., Herrera, A.J., Carreno-Muller, E., et al. (2010). Degeneration of dopaminergic neurons induced by thrombin injection in the substantia nigra of the rat is enhanced by dexamethasone: role of monoamine oxidase enzyme. *Neurotoxicology*, Vol.31, No.1, Jan 2010, pp. (55-66).

Avola, R., Di Tullio, M.A., Fisichella, A., et al. (2004). Glial fibrillary acidic protein and vimentin expression is regulated by glucocorticoids and neurotrophic factors in primary rat astroglial cultures. *Clin Exp Hypertens*, Vol.26, No.4, May 2004, pp. (323-33).

Bender, B.G., Lerner, J.A., & Poland, J.E. (1991). Association between corticosteroids and psychologic change in hospitalized asthmatic children. *Ann Allergy*, Vol.66, No.5, May 1991, pp. (414-9).

Bentson, J., Reza, M., Winter, J., et al. (1978). Steroids and apparent cerebral atrophy on computed tomography scans. *JComput Assist Tomogr*, Vol.2, No.1, Jan 1978, pp. (16-23).

Black, H.E. (1988). The effects of steroids upon the gastrointestinal tract. *Toxicol Pathol*, Vol.16, No.2, 1988, pp. (213-22).

Bohn, M.C., Howard, E., Vielkind, U., et al. (1991). Glial cells express both mineralocorticoid and glucocorticoid receptors. *J Steroid Biochem Mol Biol*, Vol.40, No.1-3, 1991, pp. (105-11).

Bridges, N., Slais, K., & Sykova, E. (2008). The effects of chronic corticosterone on hippocampal astrocyte numbers: a comparison of male and female Wistar rats. *Acta Neurobiol Exp (Wars)*, Vol.68, No.2, 2008, pp. (131-8).

Buckingham, J.C. (2006). Glucocorticoids: exemplars of multi-tasking. *Br JPharmacol*, Vol.147 Suppl 1, Jan 2006, pp. (S258-68).

Crossin, K.L., Tai, M.H., Krushel, L.A., et al. (1997). Glucocorticoid receptor pathways are involved in the inhibition of astrocyte proliferation. *Proc Natl Acad Sci U S A*, Vol.94, No.6, Mar 18 1997, pp. (2687-92).

Cucullo, L., Hallene, K., Dini, G., et al. (2004). Glycerophosphoinositol and dexamethasone improve transendothelial electrical resistance in an in vitro study of the blood-brain barrier. *Brain Res*, Vol.997, No.2, Feb 6 2004, pp. (147-51).

Chen, X., Hu, X., Zou, Y., et al. (2009). Combined treatment with minocycline and prednisone attenuates experimental autoimmune encephalomyelitis in C57 BL/6 mice. *JNeuroimmunol*, Vol.210, No.1-2, May 29 2009, pp. (22-9).

de Kloet, E.R. (2003). Hormones, brain and stress. *Endocr Regul*, Vol.37, No.2, Jun 2003, pp. (51-68).

de Kloet, E.R., Oitzl, M.S., & Joels, M. (1999). Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci*, Vol.22, No.10, Oct 1999, pp. (422-6).

De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., et al. (1998). Brain corticosteroid receptor balance in health and disease. *Endocr Rev*, Vol.19, No.3, Jun 1998, pp. (269-301).

de Sousa, N.G., Santa-Marta, C., & Morais-Almeida, M. (2010). Systemic corticosteroid hypersensitivity in children. *JInvestig Allergol Clin Immunol*, Vol.20, No.6, 2010, pp. (529-32).

Emgard, M., Paradisi, M., Pirondi, S., et al. (2007). Prenatal glucocorticoid exposure affects learning and vulnerability of cholinergic neurons. *Neurobiol Aging*, Vol.28, No.1, Jan 2007, pp. (112-21).

Fietta, P., Fietta, P., & Delsante, G. (2009). Central nervous system effects of natural and synthetic glucocorticoids. *Psychiatry Clin Neurosci*, Vol.63, No.5, Oct 2009, pp. (613-22).

Glybina, I.V., Kennedy, A., Ashton, P., et al. (2010). Intravitreous delivery of the corticosteroid fluocinolone acetonide attenuates retinal degeneration in S334ter-4 rats. *Invest Ophthalmol Vis Sci*, Vol.51, No.8, Aug 2010, pp. (4243-52).

Gomez, C.M., Higuero, N.C., Moral de Gregorio, A., et al. (2002). Urticaria-angioedema by deflazacort. *Allergy*, Vol.57, No.4, Apr 2002, pp. (370-1).

Gonzalez-Castaneda, R.E., Castellanos-Alvarado, E.A., Flores-Marquez, M.R., et al. (2007). Deflazacort induced stronger immunosuppression than expected. *Clin Rheumatol*, Vol.26, No.6, Jun 2007, pp. (935-40).

Gonzalez-Perez, O., & Alvarez-Buylla, A. (2011). Oligodendrogenesis in the subventricular zone and the role of epidermal growth factor. *Brain Res Rev*, Jan 12 2011, pp.

Gonzalez-Perez, O., Luquin, S., Garcia-Estrada, J., et al. (2007). Deflazacort: a glucocorticoid with few metabolic adverse effects but important immunosuppressive activity. *Adv Ther*, Vol.24, No.5, Sep-Oct 2007, pp. (1052-60).

Gonzalez-Perez, O., Ramos-Remus, C., Garcia-Estrada, J., et al. (2001). Prednisone induces anxiety and glial cerebral changes in rats. *JRheumatol*, Vol.28, No.11, Nov 2001, pp. (2529-34).

Hansson, E. (1989). Regulation of glutamine synthetase synthesis and activity by glucocorticoids and adrenoceptor activation in astroglial cells. *Neurochem Res*, Vol.14, No.6, Jun 1989, pp. (585-7).

Hara, K., Watanabe, K., Miyazaki, S., et al. (1981). Apparent brain atrophy and subdural hematoma following ACTH therapy. *Brain Dev*, Vol.3, No.1, 1981, pp. (45-9).

Hauser, J., Dettling-Artho, A., Pilloud, S., et al. (2007). Effects of prenatal dexamethasone treatment on postnatal physical, endocrine, and social development in the common marmoset monkey. *Endocrinology*, Vol.148, No.4, Apr 2007, pp. (1813-22).

Hauser, J., Feldon, J., & Pryce, C.R. (2006). Prenatal dexamethasone exposure, postnatal development, and adulthood prepulse inhibition and latent inhibition in Wistar rats. *Behav Brain Res*, Vol.175, No.1, Nov 25 2006, pp. (51-61).

Haynes, L.E., Griffiths, M.R., Hyde, R.E., et al. (2001). Dexamethasone induces limited apoptosis and extensive sublethal damage to specific subregions of the striatum and hippocampus: implications for mood disorders. *Neuroscience*, Vol.104, No.1, 2001, pp. (57-69).

Hill, J.E., Makky, K., Shrestha, L., et al. (2010). Natural and synthetic corticosteroids inhibit uptake(2)-mediated transport in CNS neurons. *Physiol Behav*, Nov 21 2010, pp.

Hoppmann, J., Perwitz, N., Meier, B., et al. (2010). The balance between gluco- and mineralo-corticoid action critically determines inflammatory adipocyte responses. *J Endocrinol*, Vol.204, No.2, Feb 2010, pp. (153-64).

Hu, W., Zhang, M., Czeh, B., et al. (2010). Stress impairs GABAergic network function in the hippocampus by activating nongenomic glucocorticoid receptors and affecting the integrity of the parvalbumin-expressing neuronal network. *Neuropsychopharmacology*, Vol.35, No.8, Jul 2010, pp. (1693-707).

Huang, W.L., Harper, C.G., Evans, S.F., et al. (2001a). Repeated prenatal corticosteroid administration delays astrocyte and capillary tight junction maturation in fetal sheep. *Int JDev Neurosci*, Vol.19, No.5, Aug 2001a, pp. (487-93).

Huang, W.L., Harper, C.G., Evans, S.F., et al. (2001b). Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. *Int JDev Neurosci*, Vol.19, No.4, Jul 2001b, pp. (415-25).

Ihrie, R.A., & Alvarez-Buylla, A. (2008). Cells in the astroglial lineage are neural stem cells. *Cell Tissue Res*, Vol.331, No.1, Jan 2008, pp. (179-91).

Ji, B., Li, M., Budel, S., et al. (2005). Effect of combined treatment with methylprednisolone and soluble Nogo-66 receptor after rat spinal cord injury. *Eur J Neurosci*, Vol.22, No.3, Aug 2005, pp. (587-94).

Keenan, P.A., Jacobson, M.W., Soleymani, R.M., et al. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology*, Vol.47, No.6, Dec 1996, pp. (1396-402).

Kettenmann, H., & Ransom, B.R. (2005). Neuroglia. Oxford University Press, New York.

King, D.J., Brunton, J., & Barr, R.D. (1988). The influence of corticosteroids on human erythropoiesis. An in vivo study. *Am J Pediatr Hematol Oncol*, Vol.10, No.4, Winter 1988, pp. (313-5).

Krushel, L.A., Tai, M.H., Cunningham, B.A., et al. (1998). Neural cell adhesion molecule (N-CAM) domains and intracellular signaling pathways involved in the inhibition of astrocyte proliferation. *Proc Natl Acad Sci U S A*, Vol.95, No.5, Mar 3 1998, pp. (2592-6).

Lambert, K.G., Gerecke, K.M., Quadros, P.S., et al. (2000). Activity-stress increases density of GFAP-immunoreactive astrocytes in the rat hippocampus. *Stress*, Vol.3, No.4, Nov 2000, pp. (275-84).

Liberman, A.C., Castro, C.N., Noguerol, M.A., et al. (2010). Molecular Mechanisms of Glucocorticoids Action: From Basic Research to Clinical. *Current Immunology Reviews*, Vol.6, No.4, 2010, pp. (371-380).

Liu, W.L., Lee, Y.H., Tsai, S.Y., et al. (2008). Methylprednisolone inhibits the expression of glial fibrillary acidic protein and chondroitin sulfate proteoglycans in reactivated astrocytes. *Glia*, Vol.56, No.13, Oct 2008, pp. (1390-400).

Lowenberg, M., Tuynman, J., Bilderbeek, J., et al. (2005). Rapid immunosuppressive effects of glucocorticoids mediated through Lck and Fyn. *Blood*, Vol.106, No.5, Sep 1 2005, pp. (1703-10).

Lowenberg, M., Verhaar, A.P., Bilderbeek, J., et al. (2006). Glucocorticoids cause rapid dissociation of a T-cell-receptor-associated protein complex containing LCK and FYN. *EMBO Rep*, Vol.7, No.10, Oct 2006, pp. (1023-9).

Marques, A.H., Silverman, M.N., & Sternberg, E.M. (2009). Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. *Ann N Y Acad Sci*, Vol.1179, Oct 2009, pp. (1-18).

McArthur, S., McHale, E., Dalley, J.W., et al. (2005). Altered mesencephalic dopaminergic populations in adulthood as a consequence of brief perinatal glucocorticoid exposure. *J Neuroendocrinol*, Vol.17, No.8, Aug 2005, pp. (475-82).

McLeod, J.D., & Bolton, C. (1995). Dexamethasone induces an increase in intracellular and membrane-associated lipocortin-1 (annexin-1) in rat astrocyte primary cultures. *Cell Mol Neurobiol*, Vol.15, No.2, Apr 1995, pp. (193-205).

Navarro Llanos, A., Elizalde Eguinoa, J., Boto de los Bueys, B., et al. (1996). [Toxic epidermal necrolysis in a patient treated with high doses of deflazacort]. *Med Clin (Barc)*, Vol.106, No.15, Apr 20 1996, pp. (599).

Neigh, G.N., Owens, M.J., Taylor, W.R., et al. (2010). Changes in the vascular area fraction of the hippocampus and amygdala are induced by prenatal dexamethasone and/or adult stress. *J Cereb Blood Flow Metab*, Vol.30, No.6, Jun 2010, pp. (1100-4).

Nichols, N.R., Agolley, D., Zieba, M., et al. (2005). Glucocorticoid regulation of glial responses during hippocampal neurodegeneration and regeneration. *Brain Res Brain Res Rev*, Vol.48, No.2, Apr 2005, pp. (287-301).

Niu, H., Hinkle, D.A., & Wise, P.M. (1997). Dexamethasone regulates basic fibroblast growth factor, nerve growth factor and S100beta expression in cultured hippocampal astrocytes. *Brain Res Mol Brain Res*, Vol.51, No.1-2, Nov 1997, pp. (97-105).

O'Callaghan, J.P., Brinton, R.E., & McEwen, B.S. (1991). Glucocorticoids regulate the synthesis of glial fibrillary acidic protein in intact and adrenalectomized rats but do not affect its expression following brain injury. *JNeurochem*, Vol.57, No.3, Sep 1991, pp. (860-9).

Pousset, F., Cremona, S., Dantzer, R., et al. (1999). Interleukin-4 and interleukin-10 regulate IL1-beta induced mouse primary astrocyte activation: a comparative study. *Glia*, Vol.26, No.1, Mar 1999, pp. (12-21).

Prager, E.M., Brielmaier, J., Bergstrom, H.C., et al. (2010). Localization of mineralocorticoid receptors at mammalian synapses. *PLoS One*, Vol.5, No.12, 2010, pp. (e14344).

Rachid, R., Leslie, D., Schneider, L., et al. (2011). Hypersensitivity to systemic corticosteroids: an infrequent but potentially life-threatening condition. *J Allergy Clin Immunol*, Vol.127, No.2, Feb 2011, pp. (524-8).

Ramos-Remus, C., Gonzalez-Castaneda, R.E., Gonzalez-Perez, O., et al. (2002). Prednisone induces cognitive dysfunction, neuronal degeneration, and reactive gliosis in rats. *J Investig Med*, Vol.50, No.6, Nov 2002, pp. (458-64).

Reagan, L.P., Rosell, D.R., Wood, G.E., et al. (2004). Chronic restraint stress up-regulates GLT-1 mRNA and protein expression in the rat hippocampus: reversal by tianeptine. *Proc Natl Acad Sci U S A*, Vol.101, No.7, Feb 17 2004, pp. (2179-84).

Rozovsky, I., Laping, N.J., Krohn, K., et al. (1995). Transcriptional regulation of glial fibrillary acidic protein by corticosterone in rat astrocytes in vitro is influenced by the duration of time in culture and by astrocyte-neuron interactions. *Endocrinology*, Vol.136, No.5, May 1995, pp. (2066-73).

Sabolek, M., Herborg, A., Schwarz, J., et al. (2006). Dexamethasone blocks astroglial differentiation from neural precursor cells. *Neuroreport*, Vol.17, No.16, Nov 6 2006, pp. (1719-23).

Sandau, U.S., & Handa, R.J. (2007). Glucocorticoids exacerbate hypoxia-induced expression of the pro-apoptotic gene Bnip3 in the developing cortex. *Neuroscience*, Vol.144, No.2, Jan 19 2007, pp. (482-94).

Schimmer, B.P., & George, S.R. (1998). Adrenocortical steroid hormones. In *Principles of medical pharmacology*, (Kalant, H., et al., Eds.), pp. 634-646. Saunders Elsevier, Toronto.

Schmidt, L.A., Fox, N.A., Goldberg, M.C., et al. (1999). Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. *Psychoneuroendocrinology*, Vol.24, No.4, May 1999, pp. (461-83).

Silverman, M.N., Pearce, B.D., Biron, C.A., et al. (2005). Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol*, Vol.18, No.1, 2005, pp. (41-78).

Spataro, L., Dilgen, J., Retterer, S., et al. (2005). Dexamethasone treatment reduces astroglia responses to inserted neuroprosthetic devices in rat neocortex. *Exp Neurol*, Vol.194, No.2, Aug 2005, pp. (289-300).

Tegethoff, M., Pryce, C., & Meinlschmidt, G. (2009). Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-

adrenal axis function in humans: a systematic review. *Endocr Rev*, Vol.30, No.7, Dec 2009, pp. (753-89).

Thacker, H. (2010). Glucocorticoid-induced osteoporosis. *Cleve Clin JMed*, Vol.77, No.12, Dec 2010, pp. (843; author reply 843-4).

Trousson, A., Makoukji, J., Petit, P.X., et al. (2009). Cross-talk between oxysterols and glucocorticoids: differential regulation of secreted phopholipase A2 and impact on oligodendrocyte death. *PLoS One*, Vol.4, No.11, 2009, pp. (e8080).

Ullian, M.E. (1999). The role of corticosteriods in the regulation of vascular tone. *Cardiovasc Res*, Vol.41, No.1, Jan 1999, pp. (55-64).

Van den Hove, D.L., Steinbusch, H.W., Bruschettini, M., et al. (2006). Prenatal stress reduces S100B in the neonatal rat hippocampus. *Neuroreport*, Vol.17, No.10, Jul 17 2006, pp. (1077-80).

Vardimon, L., Ben-Dror, I., Avisar, N., et al. (1999). Glucocorticoid control of glial gene expression. *JNeurobiol*, Vol.40, No.4, Sep 15 1999, pp. (513-27).

Vielkind, U., Walencewicz, A., Levine, J.M., et al. (1990). Type II glucocorticoid receptors are expressed in oligodendrocytes and astrocytes. *J Neurosci Res*, Vol.27, No.3, Nov 1990, pp. (360-73).

Wolkowitz, O.M. (1994). Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology*, Vol.19, No.3, 1994, pp. (233-55).

Xu, J., Chen, S., Chen, H., et al. (2009). STAT5 mediates antiapoptotic effects of methylprednisolone on oligodendrocytes. *JNeurosci*, Vol.29, No.7, Feb 18 2009, pp. (2022-6).

Zschocke, J., Bayatti, N., Clement, A.M., et al. (2005). Differential promotion of glutamate transporter expression and function by glucocorticoids in astrocytes from various brain regions. *JBiol Chem*, Vol.280, No.41, Oct 14 2005, pp. (34924-32).

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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