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Review Article

An overview of animal models induced by glucocorticoids

Azadeh Mesripour, Mansooreh Asghari-Varzaneh, Leila Safaeian*

Department of Pharmacology and Toxicology, Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Glucocorticoids are widely employed for treating various disorders, but their administration is associated with multiple adverse effects. To study and understand these side effects, preclinical animal models have been developed. Experimental models that replicate essential aspects of human diseases offer valuable tools for assessing potential therapeutic agents and elucidating molecular and cellular pathways in a controlled environment. In this review, we provide an overview of various animal models in which glucocorticoids have been utilized to induce humanlike disorders across different body systems. These disorders encompass hypertension, skin atrophy, hair loss, insulin resistance, dyslipidemia, gastric mucosal damage, growth retardation, muscle atrophy, osteoporosis, osteonecrosis, depression-like behavior, glaucoma, and cataracts.

Keywords:
Animal Experimentation
Glucocorticoid
Mice
Model
Rat

Introduction

Glucocorticoids (GCs) are a main type of steroid hormones that play a crucial role in the functioning of mammalian cells. Cortisol (hydrocortisone), primarily produced in the adrenal gland cortex, is the most abundant GC in humans. Various physiological actions such as glucose and fat metabolism, homeostasis, mood and cognitive performance, and the functioning of vital systems such as the immune, cardiovascular and reproductive systems are governed by this hormone (Timmermans et al., 2019).

Numerous synthetic GCs with different potencies and pharmacokinetic profiles, such as prednisolone, methylprednisolone, betamethasone, dexamethasone, fluticasone, etc., have been developed to address a range of health issues. GCs are currently the most effective medications for treating inflammatory and autoimmune diseases, along with various other disorders. Nevertheless, the administration of GCs is associated with multiple adverse effects, particularly during prolonged uses of high doses due to their broad-ranging impact on numerous organs and regulation of key endocrine system functions. These extensive and potentially harmful side effects, including cardiovascular disorders, hyperglycemia, osteoporosis, glaucoma, infections, etc., can limit the use of GCs and exacerbate a patient's health

* Corresponding author: Leila Safaeian, leila_safaeian@pharm.mui.ac.ir
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problems (Timmermans et al., 2019). Currently, many of these adverse effects are being considered for the development of pre-clinical animal models. These models aim to elucidate the mechanisms underlying the unwanted actions of GCs and evaluate the effects of novel pharmacological agents on various systemic and endocrine disorders. This review will provide an overview of different animal models in which GCs have been used to induce human-like disorders in various body systems and will discuss the possible underlying mechanisms (Figure 1 and Table 1).

Cardiovascular System

Hypertension

Hypertension is a common occurrence in Cushing's syndrome and with chronic exposure to exogenous corticosteroids. What sets this high blood pressure apart is its early onset and its tendency to persist for several years. It affects approximately 70–85% of adults and 50–78% of children with endogenous Cushing's syndrome, as well as around 20% of patients who have been on long-term corticosteroid treatment (Isidori et al., 2015). Most patients experience mild-to-moderate hypertension, while a severe form may affect 17% (Cicala and Mantero, 2010).

Various mechanisms have been proposed for GCs-induced hypertension, including oxidative stress, increasing sensitivity of vascular smooth muscle cells to vasoconstrictors, heightened activity of the sympathetic nervous system, elevated plasma levels of renin substrate and endothelin, along with reduced levels of vasodilator hormones and nitric oxide (Ong et al., 2009; Sato et al., 1992, Dubey et al., 2017; 1992; Kumai et al., 2000).

GCs play a significant role in blood pressure regulation in animals. GCs receptors are broadly present in tissues relevant to blood pressure control, such as the brain, renal, and vascular tissues (Ong et al., 2009). For instance, oral administration of hydrocortisone (8 mg/kg twice/day for 12 weeks) in dogs has been linked to

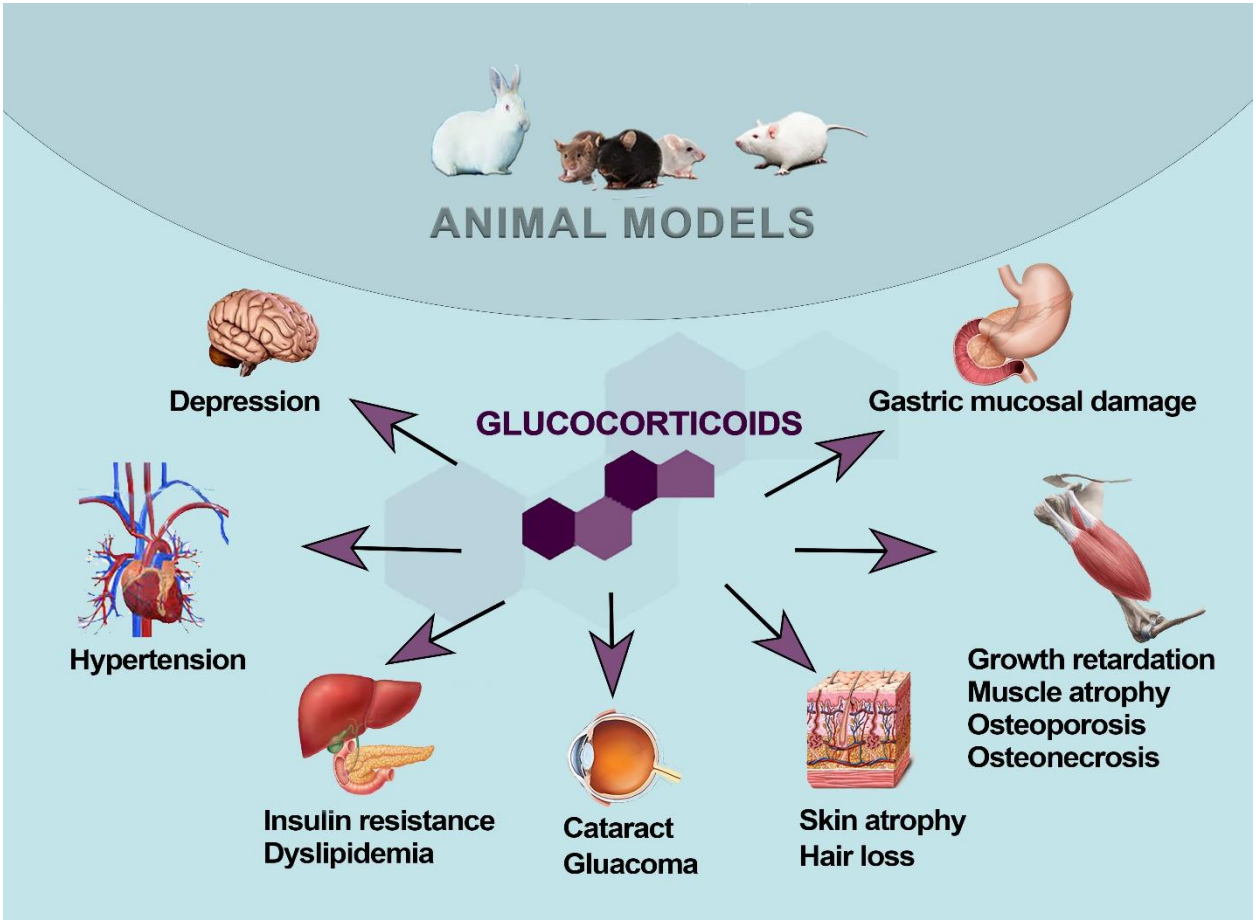

FIGURE 1. A schematic drawing of different animal models in which glucocorticoids are used for induction of human disorders in different body systems.

TABLE 1: A summary of various animal models induced by glucocorticoids.

Animal species	GC type	Dosage and administration	Reference
GC-induced hypertension			
Dog, Beagle	Hydrocortisone	8 mg/kg twice/day for 12 weeks, orally	Schellenberg et al, 2008
Rat, Wistar	Methylprednisolone	20 mg/kg/week for 4 weeks, s.c.	Kohlmann et al, 1981
Rat, Wistar; Sprague-Dawley	Dexamethasone	10-30 µg/kg/day for 2-8 weeks, s.c.	Dubey et al, 2017; Safaeian et al, 2015; Li et al, 1997
Rat, Wistar	Dexamethasone	1 mg/kg/day for 10 days, s.c.	Kumai et al, 2000
Rat, Wistar	Dexamethasone	2.5 mg/L in drinking water for 8 days, orally	Okuno et al, 1981
Dog, Mongrel	Dexamethasone	0.5 mg/kg/day for 10 days, orally	Nakamoto et al, 1991
GC-induced skin atrophy			
Rats, Hairless hr/hr	0.01% Methylprednisolone aceponate	75 µl on 9 cm^2 once daily for 5-19 days, topically on dorsal skin	Mirshahpanah et al, 2007
Rat, Sprague-Dawley	Hydrocortisone, Hydrocortisone butyrate, Dexamethasone, Budesonide, Prednisolone, Betamethasone, Triamcinolone acetonide	10 µL for 12 days, topically on the flank	Young et al, 1977
Rat, Sprague-Dawley	1% Hydrocortisone cream, 0.1% Betamethasone valerate cream, 0.025% Betamethasone benzoate cream, 0.05% Flurandrenolide cream, 0.05% Fluocinonide cream, 0.1% Dexamethasone cream, 0.03% Flumethasone pivalate cream	0.1 g for 28 days, topically on the flank	Smith et al, 1976
Rat, albino	0.05% Clobetasol propionate cream	0.25 g/kg once a day for 15 days, topically	Fawzy et al, 2019
Mouse, C57BL-6	Fluocinolone acetonide	1 µg every 72 h for 14 days, topically	Agarwal et al, 2019
GC-induced hair loss			
Mouse, C57BL-6	0.1% Dexamethasone-21-acetate	0.8-1 mL, once daily from days 9-13 post-depilation, topically on the back	Paus et al, 1994
Mouse, C57BL-6	0.05% Betamethasone	once daily starting at the time of anagen induction for 14 days, topically over truncal skin	Stenn et al, 1993
GC-induced insulin resistance			
Rat, Wistar	Dexamethasone	1 mg/kg/day for 5-10 days, i.p.	Motta et al, 2015; Martínez et al, 2016
Rat, Sprague-Dawley	Dexamethasone	1.5 mg/kg for 6 days, i.m.	Olefsky et al, 1975
Rat, Sprague-Dawley	Corticosterone	4×100 mg pellets implanted s.c. + high-fat diet for 16 days	Shpilberg et al, 2012

Animal species	GC type	Dosage and administration	Reference
GC-induced dyslipidemia			
Rat, Wistar	Dexamethasone	10 mg/kg/day for 7 days, s.c.	Safaeian et al, 2018; Mahendran and Devi, 2001
Rat, Wistar	Methylprednisolone succinate	50 mg/kg single dose, i.m.	Hazra et al, 2008
Rat, Sprague-Dawley	Corticosterone	2×150 mg pellets implanted s.c. for 10 days	Campbell et al, 2011
GC-induced gastric mucosal damage			
Rat, Wistar	Dexamethasone	4 mg/kg/day for 4 days, s.c.	Wallace, 1987
Rat, Wistar	Prednisolone-21-sodium succinate	50 mg/kg for 6 days, s.c.	Wallace, 1987
Rat, Wistar	Dexamethasone	1 mg/kg single dose, i.m. + pylorus or esophagus ligation	Bandyopadhyay et al, 1999
Rat, Wistar	Dexamethasone	0.4- 4 mg kg/day for1- 6 days, i.p.	Filep et al, 1992
GC-induced growth retardation			
Mouse, FVB	Dexamethasone	2 or 20 µg/kg/day, 5 days/week for 4 weeks; 2 mg/kg/day for 7 days, s.c.	Rooman et al, 2017; Smink et al, 2002
Mouse, BL6	Dexamethasone	5 mg/kg/day for 7 days, s.c.	Owen et al, 2009
Rat, Sprague-Dawley	Dexamethasone	40 µg/kg/day for 24 days, i.p.; 5 mg/kg/day for 7 days, s.c.	Tulipano et al, 2007; Chrysis et al. 2003
Rat, Wistar	Fluticasone propionate	250 µg for 10 days, inhaled	Kemer et al, 2015
Rat, Wistar	Methylprednisolone	1, 3, 6, 9 mg/kg/day for 90 days, s.c.	Ortoft et al. 1998b
Rat, Wistar	Corticosterone	40 mg/kg/day for 3 weeks, s.c.	Silvestrini et al. 2000
Rat, Wistar	Prednisolone	5 mg/kg/day for 80 days, s.c.	Ortoft et al. 1998a
Rabbit, New Zealand	Dexamethasone	0.24 to 0.62 mg/kg/day (20 µl, 10 times daily over 13 hour) for 8 weeks, eye drops	Kugelberg et al. 2005
Rabbit, New Zealand	Dexamethasone	80 ng/µl (1 µl/hour) over 7 days, local infusion into one proximal tibial	Baron et al. 1992
Piglet, Yorkshire	Dexamethasone	0.5, 0.3, 0.2 mg/kg/d for 14 days, oral gavage	Ward et al. 1998
GC-induced muscle atrophy			
Rat, Sprague-Dawley	Prednisolone	5 mg/kg/day for 5 days, s.c.	Eason et al, 2000
Rat, Sprague-Dawley	Triamcinolone acetonide	5 mg/kg/day for 9 days, i.p.	Lee et al, 2001
Rat, Sprague-Dawley	Dexamethasone	600 µg/kg/day for 5 days, i.p.	Noh et al, 2014; Yamamoto et al, 2010
Rat, Wistar	Dexamethasone	2 mg/kg/day for 2 weeks, s.c.	Hedya et al, 2019; Konno, 2005

Animal species	GC type	Dosage and administration	Reference
GC-induced osteoporosis			
Mouse, Swiss Webster	Prednisolone	5 mg/kg for 60 days, s.c. pellet	Yao et al, 2008
Mouse, C57BL/6J	Prednisolone	1.4, 2.1 mg/kg for 28 days, s.c. pellet	Sato et al, 2016
Mouse, CD1 Swiss	Corticosterone	15 mg/kg/day for 28 days, s.c. pellet	Herrmann et al, 2009
Mouse, BALB/c	Dexamethasone	1, 5, 10 mg/kg/day for 14-28 days, i.p.	McLaughlin et al, 2002
Rat, Wistar	Prednisolone	15 mg/kg/day every other day for 42 days, oral gavage	Yokote et al, 2008
Rat, Wistar	Methylprednisolone	1 mg/kg/day weekly for 42 days, s.c.	Wimalawansa and Simmons 1998
Rat, Sprague-Dawley	Prednisolone	1.5, 3.0 and 6.0 mg/kg/day for 90 days, oral gavage	Lin et al, 2014
Rat, Sprague-Dawley	Methylprednisolone	30 mg/kg/day for 60 days, s.c.	Bitto et al. 2009
Rat, Sprague-Dawley	Dexamethasone	0.7 mg/kg/day twice a week for 42 days, i.m.	Jiang et al. 2016
Rabbit, New Zealand	Methylprednisolone	1 mg/kg/day for 56 days; 2 mg/kg/day for 28 days, i.m.	Baofeng et al, 2010; Lin et al. 2016
Rabbit, New Zealand	Dexamethasone	0.9 mg/kg/day twice a week for 84 days, i.m.	Yongtao et al, 2014
GC-induced osteonecrosis			
Rabbit, New Zealand	Methylprednisolone	20 mg/kg/day, 3 doses, i.m. + 10 µg/kg lipopolysaccharide, single dose, i.v.	Zhang et al, 2009
Rabbit, Japanese	Methylprednisolone	10 µg/kg/day, 3 doses, i.m. + 100 µg/kg lipopolysaccharide, 2 doses, i.v.	Yamamoto et al, 1995
Rabbit, Japanese	Methylprednisolone	20 mg/kg/day, single dose, i.m.	Yamamoto et al, 1997
Rabbit, New Zealand	Methylprednisolone	10 µg/kg, single dose, i.v.	Sheng et al, 2009
Rat, Sprague-Dawley	Methylprednisolone	40 mg/kg/day, 3 doses, i.m. + 10 mL/kg/week human serum for 2 weeks, i.p.	Bekler et al, 2007
Rat, Sprague-Dawley	Methylprednisolone	100 mg/kg/day for 3 days followed by 40 mg/kg, 3 times/week, i.p., 2-6 weeks after 0.2 mg/kg lipopolysaccharide single dose, i.v.	Zheng et al, 2018
Mouse, BALB/cJ	Dexamethasone	4 mg/L for 12 weeks, orally in drinking water	Yang et al, 2009
Pig, Domestic	Methylprednisolone	30 mg/kg bolus, followed by 5.4 mg/kg/h for further 23 h, i.v.	Drescher et al, 2004
Chickens, Leghorn	Methylprednisolone	3 mg/kg/week for 6-12 weeks, i.m.	Wang et al, 2000

Animal species	GC type	Dosage and administration	Reference
GC-induced depression			
Rat, Lister	Corticosterone	100 mg for 1 week, s.c. pellet	Fernandes et al, 1997
Rat, Wistar	Corticosterone	40 mg/kg for 1 month, s.c.	Sousa et al, 2000
Mouse, C57BL/6	Corticosterone	20 mg/kg for 21 days, s.c.	Ma et al, 2018
Mouse, Swiss	Dexamethasone	64 µg/kg, single dose or 16 µg/kg for 14 days, s.c.	Wróbel et al, 2015
Mouse, NMRI	Dexamethasone	15, 60 or 250 µg/kg, single dose or 15 µg/kg for 7 days, s.c.	Mesripour et al, 2019
Mouse, C57BL/6	Prednisolone	50 or 100 mg/kg for 6 or 7 days, s.c.	Kajiyama et al, 2010
GC-induced glaucoma			
Mouse, C57BL/6J	Dexamethasone	20 µL/eye, once a week for 10 weeks, periocular	Maddineni et al, 2020
Mouse, C57BL/6J	Dexamethasone phosphate (0.1%)	3 times/day for 6 weeks, topical ocular	Zode et al, 2014
Mouse, C57BL/6J	Dexamethasone	3-4 mg/kg/day for 3-4 weeks, s.c. osmotic mini-pumps	Overby et al, 2014
Mouse, C57BL/6	Triamcinolone acetonide	40 mg/mL (20 µL bolus) subconjunctivally	Kumar et al, 2013
Rat, Wistar	Dexamethasone (0.1%)	4 times/day for 1, 2 and 4 weeks, topical ocular	Sawaguchi et al, 2005
Rabbit, New Zealand	Dexamethasone 21-phosphate, Betamethasone 17-valerate	0.1 ml/0.5 mg (Dexamethasone), 0.1 ml/4 mg (Betamethasone), subconjunctivally	Song et al, 2011
Rabbit, New Zealand	0.1% Dexamethasone, 1% Rimexolone, 0.5% Loteprednol etabonate, 0.1% Fluorometholone	4 times/day for 1 month, topical ocular	Qin et al, 2010
GC-induced cataract			
Rabbit, Dutch Belt	Triamcinolone acetonide, Fluocinolone acetonide	2 mg (Triamcinolone), 1 mg (Fluocinolone), intravitreally	Hernandez-Denlinger et al, 1985
Rabbit, New Zealand	Dexamethasone, Prednisolone, Cortisol	20-200 nmol/0.2 mL, intravitreally	Bucala et al, 1985
Rabbit, New Zealand	1.5% cortisone acetate, 0.2% hydrocortisone, 0.1% Dexamethasone	3 times/day for 4-6 months, topical ocular	Wood et al, 1967
Rat, Brown Norway	Prednisolone	1% solution topical drop or 10 mg/kg/day, 3 times pulse/2 months for 16 months, i.v. pulse	Nagai et al, 2004
Chick Embryo	Dexamethasone, Hydrocortisone, Prednisolone	0.25 µM in culture system	Kosano H, Nishigori, 2002

mild but significant increases in systemic blood pressure (Schellenberg et al., 2008). In a study by Kohlmann et al., rats exhibited significant increases in mean arterial pressure after receiving subcutaneous (s.c.) methylprednisolone at a dose of 20 mg/kg/week for 4 weeks (1981). Among various GCs, dexamethasone, a long-acting and potent drug, is typically used as an endocrine model of hypertension in rats to elucidate the mechanisms of GC-induced hypertension in humans. Interestingly, this form of high blood pressure is not blocked by classical glucocorticoid receptor blockers and resembles some forms of essential hypertension (Whitworth et al., 2001)

Different dexamethasone regimens have been studied, but doses ranging from 0.01-0.03 mg/kg/day, s.c. for 2-8 weeks are commonly used to induce hypertension in rats (Safaeian et al., 2015; Dubey et al., 2017; Li et al., 1997). Higher doses of dexamethasone, such as 1 mg/kg/day, s.c. for a shorter duration (2 days), have also been shown to elevate blood pressure in rats (Kumai et al., 2000). Okanu et al., adminstrated dexamethasone at a dose equivalent to 0.030-0.060 mg/kg/day orally for 8 days by adding 2.5 mg/L to the rats' drinking water to induce high blood pressure. They found that dexamethasone-induced hypertension was independent of sodium retention or aldosterone activity (1981). In a study by Nakamoto et al., dogs experienced an increase in blood pressure after oral treatment with high doses of dexamethasone (0.5 mg/kg/day) for 10 days (1991).

Although many experimental investigations have shown the hypertensive effects of corticosteroids in various laboratory animals such as dogs, sheep, mice and rats, several differences in clinical features compared to human hypertension have limited the use of certain animal species. For example, the development of resistance in kidney vasculature occurs in humans and rats, but not in sheep (Whitworth et al., 2001). Another limitation is that GC-induced hypertension is less pronounced than in other models, such as the deoxycorticosterone acetate-salt induced model, leading to only mild increases in systemic blood pressure (Lin et al., 2016). Moreover, the complexity of multiple mechanisms and compensatory responses may hinder the development of specific treatments in this hypertension model.

Dermatologic System

Skin Atrophy

Topical GCs, which are used to treat inflammatory skin diseases, can cause structural changes in skin tissue, appearing as dermal atrophy, striae atrophicans, rubeosis iridis, acne, purpura, delayed lesion healing, and, to a lesser extent, hypertrichosis. The most common side effect resulting from both topical and systemic GC therapy is skin atrophy. This involves alterations in the skin's architecture, including a reduction in dermal cells, loss of elasticity, increased brittleness, telangiectasia, bruising, and heightened skin transparency (Niculet et al., 2020; Alan and Alan, 2018). The incidence of skin atrophy is affected by factors such as the type of GCs, drug vehicle, frequency of application, treatment duration, and the area where the drug is applied (Schoepe et al., 2006).

GCs exert their catabolic and antimitogenic effects on both the dermis and epidermis (Schoepe et al., 2006; Maubec et al., 2015). They reduce the size of fibroblasts and keratinocytes, inhibit their reproduction, and hinder the synthesis of hyaluronic acid. These acttions result in a decrease in epidermal thickness, skin barrier thickness, and elasticity. Consequently, the skin becomes more permeable, leading to water and electrolyte loss (Delforno et al., 1978; Kolbe et al., 2001). GCs also facilitate water permeability through the transdermal space by affecting the lipid layeron the upper surface of the epidermis. Additionally, they have a catabolic effect on skin components such as ceramides, cholesterol, and fatty acids, disrupting the skin's protective function (Niculet et al., 2020; Shue et al., 1997). This deterioration of extracellular matrix (ECM) proteins, including fibronectin, collagen, proteoglycans, elastin, and metalloproteinases, affects the flexibility and firmness of skin (Niculet et al., 2020; Schoepe et al., 2006; Røpke et al., 2017).

In animal studies, skin atrophy induced by GCs is often investigated using dogs, pigs, mice and especially rats. Various GCs, such as hydrocortisone, hydrocortisone butyrate, dexamethasone, prednisolone, betamethasone, budesonide, and triamcinolone acetonide, all have been shown to induce dermal atrophy. Smith et al. (1976) evaluated the topical application of various GCs on rats' flank skin areas for 28 days. Skin atrophy was measured by comparing the weight of treated skin section (1.6 cm diameter) dissected from the treated area with that of the non-treated opposite area in rats after 12 days of GC application (Young et al., 1977). Fawzy et al. (2019) induced GC-induced skin atrophy in rats by applying 0.05% clobetasol propionate cream at a dosage of 0.25 g/kg once a day for 15 days. Currently, hairless animals like hr/hr rats are favorite for this purpose (Mirshahpanah et al., 2007; Schoepe et al., 2006). In mice, skin atrophy has been reported following topical administration of fluocinolone acetonide at a dose of 1 µg every 72 h for 14 days (Agarwal et al., 2019).

It's important to note that the skin atrophy model in preclinical studies has limitations in fully replicating atrophy in humans due to anatomical differences between rodent and human skin, such as the presence of large number of skin appendages and the absence of a papil-

lary dermis in rodents, that may change pharmacokinetic patterns (Schoepe et al., 2006).

Hair Loss

Hair loss, which can appear in different patterns, can be a consequence of stress or in other words, exposure to high levels of endogenous or exogenous GCs. According to the report of European Registry on Cushing's syndrome, 31% of people with Cushing's syndrome suffer from hair loss. Additionally, excess and prolonged use of systemic corticosteroids increases the incidence of hair loss (Lee and et al., 2017). However, topical forms of GCs are extensively employed as the first-line treatment for conditions like alopecia areata due to their anti-inflammatory properties (Amin and Sachdeva, 2013).

Some GCs such as dexamethasone, have been reported to Activate apoptotic signals and have an inhibitory effect on various growth factors in dermal papilla and hair follicle cells (Kwack et al., 2017).

Paus and co-workers introduced a mouse model for studying the regressing phase (catagen) of hair follicles based on the skin pigmentation. They achieved this by topically administrating 0.1% dexamethasone-21-acetate once a day for 5 days (on days 9-13 after depilation) on growing follicles in anagen phase, which was induced by depilation on the backs of female C57BL-6 mice. In their study, topical dexamethasone application significantly accelerated the transition tocatagen-like follicles in terms of both width and uniformity. This animal model can be valuable for investigating the molecular and cellular aspects of the catagen phase (1994). However, they had previously reported the inhibitory effect of topical betamethasone on anagen development in depilated mice, suggesting a dual action of potent GCs on the catagen phase, possibly due to the involvement of activated macrophages in hair growth (Stenn et al., 1993). Another limitation is that the therapeutic role of topical GCs in alopecia areata, through anti-inflammatory effects, may create some misperception in this model.

Endocrine and Metabolic System

Insulin Resistance

GCs play a pivotal role in regulating glucose metabolism under physiological and pathological situations. During fasting, cortisol, along with other regulatory hormones, helps maintain blood glucose levels by reducing glucose consumption and increasing its production. Prolonged and high-dosage of GC use induces fasting-like conditions, leading to insulin secretion and hyperglycemia in mammals (Lambillotte et al., 1997). This condition, known as steroid diabetes, is responsible for 2% of diabetes cases (Notman, 1984). Various in vitro and animal models have been utilized to elucidate the possible mechanisms behind the disruption of glucose homeostasis due to chronic GC use. These mechanisms involve alterations in the liver, skeletal muscles, adipose tissue, and pancreases. Administration of GCs in animals can result in the development of type 2 diabetes mellitus or metabolic syndrome. Rapid onset of diabetes symptoms has been observed when GC use is combined with a high-fat diet in a rat model (Shpilberg et al., 2012).

Motta et al. (2015) showed that intraperitoneally (i.p.) treatment of Wistar rats with dexamethasone (1 mg/kg/day for 5 days) led to elevated blood glucose and insulin levels, concurrent with insulin resistance and glucose intolerance. They reported increased glycerol secretion, reduced activity of protein kinase B, and insulin receptor substrate in epididymal adipose tissue. Changes in the expression of glucose transporters and their translocation to the plasma membrane have been found following GCs administration in some studies (Sakoda et al., 2000).

GCs promote hepatic glucose production and reduce glucose transport in peripheral tissues by upregulating the genes for phosphoenolpyruvate-carboxy kinase and glucose-6-phosphatase (Pasieka and Rafacho, 2016; Aschenbach et al., 2010). In a study by Olefsky et al. (1975) insulin binding to isolated hepatocytes decreased in rats after receiving 1.5 mg/kg dexamethasone for 6 days, while binding returned to near-normal levels with chronic low-dose usage (125 mg/kg for 21 days), possibly due to reduced insulin resistance.

Skeletal muscles are another important organ that affect the glucose homeostasis (Beaupere et al., 2021). Treatment of rats with dexamethasone (1 mg/kg/day, i.p.) resulted in a significant reduction in glucose uptake in response to insulin and glycogen synthesis in soleus and epitrochlearis muscles and epididymal adipocytes. This occurred through the downregulation of protein kinase B expression and insulin-stimulated phosphorylation (Burén et al., 2008). Other mechanisms contributing to GCs-induced insulin resistance in muscles include increased epinephrine concentration, reduced GLUT4 levels, impaired translocation of GLUT4 to the

cell membrane, dysregulation of lipid metabolism with increased lipolysis and β-oxidation, and elevated in intramuscular triglyceride levels (Kennedy et al., 1993; Ruzzin et al., 2005).

GCs also disturb adipose tissue, promoting lipolysis by upregulating the expression of lipolytic enzymes and causing the release of free fatty acids and glycerol into the bloodstream. This can result in insulin-resistance in adipose tissue due to changes in gene expression (Djurhuus et al., 2004). The release of adipokines, like leptin and adiponectin, from adipose tissue, which are contributed in glucose and lipid metabolism, appetite control, and energy balance, is also affected by GCs (Geer et al., 2014).

Pancreatic β-cells may also be influenced by GCs. While in vitro studies have shown that GCs suppress β-cells viability and their ability to produce and secret insulin, in vivo studies have yielded contradictory results due to variations in models and GC dosages (Beaupere et al., 2021). Pancreatic α-cells are also affected by GCs, leading to an increase in glucagon concentration as an adaptive response to elevated insulin levels resulting from insulin resistance (Rafacho et al., 2014). GCs also suppress glucagon-like peptide-1, a hormone that promotes the proliferation of pancreatic beta cells and reduces insulin resistance (Kappe et al., 2015).

Due to the wide role of GCs in the body, different pathways must be considered simultaneously in animal models to interpret the mechanisms underlying GC-induced insulin resistance. Additionally, it is important to note that high doses of GCs are typically required to induce diabetes in laboratory animals, often several times higher than standard laboratory animals doses (Shpilberg et al., 2012).

Dyslipidemia

Dyslipidemia is one of the metabolic changes that may occur following chronic exposure to GCs and in Cushing's syndrome. These effects on lipid metabolism include the development of typical features seen in Cushing's syndrome, which are similar to those observed in metabolic syndrome, such as obesity, insulin resistance, increased fasting blood glucose, total cholesterol, and triglycerides levels (Hazra et al., 2008).

GCs induce dyslipidemia via affecting the expression of lipoprotein receptor genes and apolipoprotein genes, as well as the production and clearance of lipoproteins and free fatty acids (Wang et al., 2012). Long time exposure to high doses of GCs can increase the formation of very-low-density lipoproteins (VLDL) in the intestine and liver, decrease the expression of LDL receptors, reduce the activity of lecithin cholesterol acetyl transferase, reduce the production of apolipoprotein E while increasing its catabolism, stimulate intravascular lipolysis of triglycerides, enhance lipoprotein lipase activity, and subsequently promote lipolysis in adipose tissue. This leds to increased levels of circulating free fatty acids (Ross and Marais, 2014; Sun et al., 2021).

Fatty liver and steatosis occur due to the motivation of AMP-activated protein kinase, decreased activity of hepatic lipoprotein lipase, augmented lipogenesis, VLDL and fatty acid synthesis, which result from increases in the activity of key lipogenic enzymes, including acetyl-CoA carboxylase and fatty acid synthase. Additionally, fatty acid β oxidation is suppressed (Arnaldi et al., 2010; Sun et al., 2021). Moreover, increased production of free radicals and oxidative damage to the liver have been described during dexamethasone-induced dyslipidemia (Safaeian et al., 2018).

In animal studies, a single dose of hydrocortisone has been shown to elevate LDL and VLDL in athero¬sclerotic rabbits (Nagornev et al., 1980). Administration of dexamethasone, triamcinolone, and methyl prednisone (but not hydrocortisone) has been associated with hypertriglyceridemia, hypercholesterolemia and increased free fatty acids in rats (Mahendran and Devi, 2001; Staels et al., 1991). However, some variations have been reported in the blood levels of HDL, LDL, VLDL, apolipoprotein A1, and apolipoprotein E (Mahendran and Devi, 2001; Staels et al., 1991).

As an established model, s.c. injection of dexamethasone (10 mg/kg/day) for about 1 week has been used to induce dyslipidemia in Wistar rats in some studies (Safaeian et al., 2018; Safaeian et al., 2018; Kumar et al., 2011).

An increase in preadipocytes differentiation, basal lipolytic rate, and increased expression and activity of lipolytic enzymes, such as hormone-sensitive lipase and adipose triglycerides lipase, have been observed in Sprague-Dawley rats after receiving s.c. implantation of pellets containing corticosterone (300 mg for 10 days) (Campbell et al., 2011). In the study by Hazra et al., the administration of 50 mg/kg methylprednisolone intramuscularly (i.m.) produced transient changes in LDL

receptor mRNA, plasma total cholesterol, and LDL in rats (2008).

The main limitation of GC-induced dyslipidemia is that the rate of lipid irregularities and the balance between lipolytic and lipogenic actions of GCs can vary widely. This variability depends on factors such as age, gender, underlying pathological conditions, type and dosage of GC, duration of treatment, and potential drug interactions (Alan and Alan, 2018). Moreover, high doses of GCs are required to induce hyperlipidemia, which may be associated with side effects such as GC-induced skeletal muscle loss and severe body weight loss in laboratory animals (Dunford and Riddell, 2016).

Gastrointestinal System

Gastric Mucosal Damage

GCs affect the stomach through a dual function. Under normal or stressful circumstances, GCs play a role in gastroprotection by maintaining gastric blood flow, reducing gastric motility and microvascular permeability, regulating short-time blood glucose levels, and thus protecting gastric mucosal integrity (Filaretova, 2011). However in pathological situations and with prolonged high-dose pharmacological use, they can lead to stomach ulcers (Filaretova et al., 2009).

Several mechanisms have been proposed to explain the pro-ulcerogenic effect of GCs. These include a reduction in the synthesis and secretion of gastric mucus and changes in its biochemical composition, inhibition of bicarbonate secretion or alkaline response, delayed gastric wound healing by inhibiting prostaglandin production, induction of gastric cell hyperplasia leading to increased acid output, and a decrease in epithelial cell turnover (Henderson and Webster, 2006).

It has been shown that daily injections of dexamethasone at the dose of 4 mg/kg or prednisolone at the dose of 50 mg/kg, s.c. for 4-6 days, are ulcerogenic in rats (Wallace, 1987). Even in non-ulcerogenic doses (0.1 or 0.2 mg/kg/day orally for 9 days), dexamethasone delayed the healing of gastric erosion in acetic acid-induced gastric ulcers in rats. This delay was attributed to its impact on the regenerative system, including a reduction in epithelial cell proliferation, mucus production, and angiogenesis at the ulcer site (Luo et al., 2003). Bandyopadhyay et al. (1999) also reported increased basal and drug-induced gastric acid secretion 24 h after treatment with dexamethasone (1 mg/kg, i.m.), which was attributed to the inhibition of peroxidase and prostaglandin synthetase in rats. In another study, treatment with dexamethasone (0.4-4 mg/kg, daily for 1-6 days) led to the significant injury to the mucosa layer of the rat stomach in a time- and dose-dependent manner, which was related to an increase in tissue platelet-activating factor levels in the stomach (Filep et al., 1992).

Musculoskeletal System

Growth Retardation

There is a concern about the reduction in growth observed in children, potentially affecting their final adult height, during long-term treatment with GCs, even when administrated in nasal and respiratory dosage forms (Skoner et al., 2000). GCs suppress the growth hormone and insulin like growth factor-1 (IGF-1) pathway through inhibition of growth hormone release, decreasing IGF-1 expression, and impairing its signaling in chondrocytes of growth plate. Additionally, GCs have other suppressive effects on chondrocytes, such as the inhibition of angiogenesis and the decomposition of ECM (Wood et al., 2018; Smink et al., 2002).

For evaluation of growth, routine weight and height (length of body or tail) measurements are performed in animal studies. Dexamethasone has been widely used to induce growth retardation in rodent models, with various dosages ranging from 0.02 to 5mg/kg/day for 7 to28 days. Totally, daily s.c. injections of dexamethasone at doses of 2–5 mg/kg yield the best results in inducing growth retardation (Wood et al., 2018). In mice, dexamethasone has been injected s.c. in 3- and 5-weeks old (Rooman et al. 2017). Male Sprague–Dawley or Wistar rats, up to 4 months old, have been used in some studies, showing varying durations of growth inhibition, from 4 to 90 days. However, rapid catabolic changes and severe weight loss resulting from high GC doses can interfere with results. Therefore, it is suggested to consider more precise parameters, such as bone length measurements or histological examination of the growth plate. Another limitation in GC-induced growth retardation studies is the variation in the timing of growth plate closure and sexual maturity based on the sex and species of laboratory animals (Wood et al., 2018).

Muscle Atrophy

Myopathy resulting from chronic administration of GCs is the most prevalent pharmacological cause of

muscle atrophy. Approximately 60% of individuals with Cushing's syndrome suffer from muscle wasting (Gupta and Gupta, 2013). Fluorinated GCs such as dexamethasone, triamcinolone, and betamethasone pose a higher risk of myopathy, however, any frequently prescribed GC can trigger myopathy (Anagnos and Ruffi, 1997). This harmful effect is primarily observed in type IIb (glycolytic) muscle fibers, while its impact on type I (oxidative) fibers is minimal (Schakman, et al., 2008).

Qualitative changes in the contractile apparatus during GC-induced myopathy include a reduction in collagen synthesis, increased degradation of myofibrillar proteins due to stimulation of ubiquitin-proteasome system, and a decrease in the synthesis rate of myosin heavy chain type II and actin (Alev et al., 2018).

Various animal experiments have been conducted to understand the mechanism of GCs-induced myopathy. For example, prednisolone injection with a dosage similar to the most common prescribed dose in the asthmatic situation (5 mg/kg/day for 5 days, s.c.) in female Sprague-Dawley rats resulted in dropping body weight, diaphragm muscle weight, and a 13% reduction in maximal specific isometric tetanic tension (Eason et al., 2000). In another study, Sprague-Dawley rats treated with triamcinolone acetonide (5 mg/kg for 9 days, i.p.) experienced an average degeneration of nearly 26% in the soleus muscle (Lee et al., 2001). Dardevet et al. (1995) showed that muscle wasting was more rapid and recovery of muscle mass was delayed in older rats after administration of dexamethasone. Dexamethasone has been used at a dosage of 600 μg/kg/day i.p. for 5 days to induce muscle atrophy in Sprague Dawley rats in some studies (Noh et al., 2014; Yamamoto et al., 2010). However, several investigations have injected dexamethasone at 2 mg/kg/day s.c. for 2 weeks in Wistar rats (Hedya et al., 2019; Konno, 2005).

One limitation of GC-induced muscle atrophy is that muscular protein metabolism is extremely dependent on muscle movement and fiber use (Garlick et al., 1989).

Osteoporosis

Chronic consumption of GCs is one of the secondary causes of osteoporosis, which has detrimental and irreversible effects on bone health. GCs can lead to bone fractures independently of a patient's previous history of fracture risk and bone mineral density (BMD). The extent of the impact depends on factors such as the prescribed GC dose, duration of treatment, age, and body weight (Alan and Alan, 2018; Wood et al., 2018).

In general, the effects of GCs on osteoporosis development occur in two stages. In the primary stage, bone destruction is initiated by osteoclasts, while the secondary slow stage involves ossification (Weinstein et al., 1998). GCs interfere with the bone remodeling cycle and disrupt the function of bone cells. They suppress the maturation and replication of osteoblasts by altering their pathways from stem cells, primarily through the stimulation of peroxisome proliferator-activated receptor-γ2 transcription factors (PPARγ) (Ohnaka et al., 2005). Supra-physiologic concentrations of GCs disturbs osteogenesis by inducing osteoblast apoptosis, diminishing osteoblast function and longevity, decreasing the synthesis of collagen type I and osteocalcin, promoting osteoblast and osteocytes death, and disturbing mineralization process (Wood et al., 2018; Alan and Alan, 2018). In addition, GCs reduce calcium uptake in the gastrointestinal tract and inhibit renal calcium re-absorption, further contributing to bone porosity (Wood et al., 2018) .

Animal studies have been performed on GCs-induced osteoporosis for evaluation of novel therapeutic agents in mice, rats, rabbits, sheep, pigs, and zebrafish. Among these, mice are considered the most suitable model due to their similarities with humans in terms of GC effects on bone tissue. GCs primarily induce bone resorption by osteoclasts and secondary impairment of osteoblast function in bone production(Wood et al., 2018).

The s.c. implantation of slow-release prednisolone pellets at a dose of 5 mg/kg for 60-days in 6-month-old male Swiss Webster mice increased osteoclast function while reducing osteoblast activity, leading to a decrease in trabecular bone volume (Yao et al., 2008). In another study, prednisolone at doses of 1.4 or 2.1 mg/kg, implanted with slow-release pellets in 4-month-old female C57BL/6J mice for 28 days, resulted in the thinning of cancellous bone trabecular and cortical bone area (Baschant et al., 2016). A dosage of prednisolone 2–5 mg/kg/day in mice gets the best result in inducing osteoporosis (Wood et al., 2018). Utilization of 3 mg/kg/day, s.c. methylprednisolone 3 times per week induced osteoporosis in female Sprague-Dawley rats (Dalle Carbonare et al., 2007). After 8 weeks of methylprednisolone treatment at a dose of 1 mg/kg/day, i.m,. in female New Zealand white rabbits, a reduction in BMD of lum-

bar spine was observed (Baofeng et al., 2010).

A limitation of GC-induced osteoporosis is that it may not occur in rats unless accompanied by a low-calcium regimen. Moreover, the guinea pig is not an ideal model for GC-induced osteoporosis due to its unique hypothalamic-pituitary-adrenal axis (Turner, 2001).

Osteonecrosis

GCs-induced osteonecrosis affects 9–40% of patients treated with GCs for an extended period, even topically. There is also a risk of this complication occurring following short-time, high dose GC use via intra-articular injections (Weinstein, 2011). Osteonecrosis mainly occurs in the femoral head and is described by a reduced trabecular width and an increased number of apoptotic osteocytes and osteoblasts (Wood et al., 2018; Boksenbaum and Mendelson, 1963).

Various factors and their interactions are identified in the pathophysiology of GCs-induced osteonecrosis including disruption in bone marrow stem cells, bone matrix, and cartilage, increased oxidative stress, abnormalities in lipid metabolism and the coagulation system, endothelial dysfunction and apoptosis of bone cells (Xie et al., 2015).

GCs promote differentiation of bone marrow stem cells into adipocytes via increasing the expression of adipogenic genes while inhibiting osteogenic differentiation through decreased expression of various osteoblast transcription factor genes. These changes result in more fat cells, elevated lipid deposition, and insufficient repair of lesions in the initial phase of osteonecrosis (Sheng et al., 2007; Li et al., 2005). Moreover, GCs cause the degeneration of bone matrix and articular cartilage, disrupt the balance between osteoblasts and osteoclasts, reduce bone formation, and induce apoptosis of bone cells during the development of osteonecrosis (Zheng et al., 2018; Takano-Murakami et al., 2009).

A key mechanism in the pathophysiology of osteonecrosis caused by corticosteroids is ischemia due to endothelial cell damage, hyperlipidemia, fat embolism, and intravascular thrombosis, vascular contraction, insufficient neovascularization, and oxidative damage (Qin et al., 2006; Kerachian et al., 2009).

The New Zealand white rabbit model is a well-known animal model for studying GC-induced osteonecrosis. In this model, a single intravenous(i.v.) administration of lipopolysaccharide (10 μg/kg) followed by three administrations of high-dose methylprednisolone (20 mg/kg/day, i.m.) after 2 to 6 weeks is associated with a high incidence of GCs-induced osteonecrosis and a low mortality rate (Zhang et al., 2009). In rats, i.p. injection of human serum (10 mL/kg/week) for 2 weeks along with three doses of methylprednisolone (40 mg/kg/day, i.m.) has been used to induce osteonecrosis (Bekler et al., 2007). In a modified model, a single dose of lipopolysaccharide (0.2 mg/kg, i.v.) followed by pulsed therapy with high-dose methylprednisolone (100 mg/kg, i.p.) as 3 injections for 3 days, followed by 40 mg/kg, i.p. three times per week during week 2 to week 6, induced clinical and histological alterations, showing a 100% incidence of osteonecrosis in Sprague–Dawley rats (Zheng et al., 2018). GCs-induced osteonecrosis models have also been established in other animals such as pig, mouse, emu, and bipedal chicken albeit with a lower incidence rate (Xie et al., 2015). However due to the small size of the mouse's femoral head, diagnosis of osteonecrosis via MRI or CT is difficult and limits the use of mice as an animal model for osteonecrosis. Moreover, many animal studies rely on histopathology to evaluate osteonecrosis, which may not always align with clinical investigations (Xu et al., 2018).

Neuropsychiatric System

Depression

Stress experience in individuals is highly related to the development of depression, and it may also contribute to the severity and recurrence of this mental illness. It is known that cortisol regulates neurogenesis, neuronal survival, and memory (Anacker et al., 2011). Patients with Cushing's disease or those treated with synthetic GCs may experience psychiatric problems similar to major depression (Brown et al., 2004).

Numbers of mechanisms are suggested for GCs-induced depression-like behavior in rodents. Administration of corticosterone, the rodent stress hormone, for one week through a 100 mg pellet implantation, has been shown to change the serotonin neurotransmitter system in male rats. This includes a decrease in 5-HT1A receptor binding in the dentate gyrus and an increase 5-HT2A receptor binding in the parietal cortex (Fernandes et al., 1997). Chronic exposure to corticosterone (40 mg/kg, 1-month) or unpredictable stress has led to reductions in hippocampal volume, alterations in neuronal structure, and changes in synapse numbers in rats (Sousa et al.,

2000; Tata and Anderson, 2010).

The development of depression due to GCs involves the inhibition of neurogenesis through reduced biosynthesis of neurotrophins like brain-derived neurotrophic factor, a decrease in tyrosine hydroxylase concentration (a rate-limiting enzyme in biosynthesis of catecholamines), mitochondrial dysfunction, and increased oxidative stress (Ridder et al., 2005; Henn et al., 2004).

As a model of GCs-induced depression, acute exposure to dexamethasone at various doses (single dose 15, 60 or 250 μ/kg, s.c.) can dose-dependently increase immobility time during the forced swimming test (FST) in male NMRI mice (Mesripour et al., 2019). By administrating the highest dose (250 μ/kg), animals remained motionless for a longer period during the FST. In addition, after administration of 15 μ/kg dexamethasone for seven consecutive days, mice showed signs of despair during the FST and anhedonia during the sucrose preference test (Mesripour et al., 2019; Mesripour and Rakhshankhah, 2021; Mesripour et al., 2021).

The main limitation is that the alterations in mood caused by GCs are more multifaceted than simple increases or decreases in GCs or their receptors. Moreover, despite many pharmacological investigations into GCs-induced depression, the theory has not been thoroughly verified in humans (Krishnan and Nestler, 2011).

Ophthalmologic System

Glaucoma

The long-term and high-dosage of GC administration induce ample ocular side effects, including the development of ocular hypertension which can initiate iatrogenic open-angle glaucoma and permanent vision loss. Studies have revealed an important connection between GCs and primary open-angle glaucoma (Patel et al., 2019).

In fact, GC-induced ocular hypertension is related to a defect in the outflow pathway induced by physical changes in microstructure of trabecular meshwork, which increases resistance to outflow and elevates intra ocular pressure (Stamer and Clerk, 2017). Raghunathan et al. (2015) reported that 4 weeks exposure to dexamethasone in primary human trabecular meshwork cells resulted in a denser deposited matrix along with elevated α-smooth muscle actin expression and upregulation of fibrotic markers through the stimulation of the mitogen-activated protein kinase (MAPK) signaling pathway. Moreover, topical treatment of rabbits with dexamethasone (0.1%) caused stiffness in trabecular meshwork tissues in their study.

It has been demonstrated that chronic endoplasmic reticulum stress is associated with trabecular meshwork dysfunction and the development of glaucoma in a mouse model (Zode et al., 2011). Experimental models of ocular hypertension include many characteristics of this disorder in humans and provide valuable insights into the pathogenesis of iatrogenic open-angle glaucoma induced by GCs.

In most animal studies, dexamethasone has been applied in topical ocular dosage forms to various species, including rabbits, cats, sheep, rats, mice, dogs, cows and non-human primates (Overby et al., 2016). The topical administration of dexamethasone phosphate (0.1%) as eye drops 3 times a day for approximately 6 weeks in C57BL/6 mice increased intraocular pressure, accompanied by retinal dysfunction and optic neuropathy, more significant than systemic application. A limitation of this model is that it needs long-term administration of eye drops 3 times a day by an expert individual (Zode et al., 2014). In another model, anesthetized C57BL/6 J mice were peri-ocularly injected with 200 μg/20 μL dexamethasone bilaterally once a week for 6 weeks, resulting in increased intraocular pressure, dysfunction of trabecular meshwork, progressive optical nerve degeneration. and physical and functional loss of retinal ganglion cells (Maddineni et al., 2020). Dexamethasone has also been delivered via osmotic minipump implanted s.c. during 4 weeks, resulting in ocular hypertension in mice (Whitlock et al., 2010). However, using minipump delivery techniques needs surgery and has limitations, including severe side effects such as weight loss (Overby et al., 2016). Moreover, triamcinolone acetonide has also been used subconjunctivally at a concentration of 40 mg/mL (20 μL bolus) to induce ocular hypertension in mice (Kumar et al., 2013).

The main limitation in murine models is the small size of their eyes and absence of a lamina cribrosa in the optic nerve (A Bouhenni et al., 2012).

Intravitreal injection of triamcinolone acetonide, alike subconjunctival injection of dexamethasone, for 30 days also increased intraocular pressure in New Zealand white rabbits, although glucose metabolism in the aqueous humor was different between these two GCs (Song et al., 2011). However, there are some anatomical

dissimilarities in the trabecular meshwork and aqueous outflow pathways between rabbits and humans, limiting the use of the rabbit glaucoma model (A Bouhenni et al., 2012).

Cataract

The chronic use of systemic, topical, and possibly inhaled GCs can cause development of posterior subcapsular cataracts. This bilaterally and gradually developing side effect of GCs may occur in a range of 22-58% of patients (Jobling and Augusteyn, 2002; Turno-Krecicka et al., 2016; Cumming et al., 1997; Skalka and Prchal, 1998). GCs initiate metabolic alterations in the lens, gradually reducing glutathione levels, causing protein adduct formation, and the accumulation of macromolecules, eventually leading to the formation of cataracts (Pescosolido et al., 2001).

The direct effects of GCs include osmotic disturbances and electrolyte imbalances, which result in vacuolization and swelling due to increased cation entry in to lens cells. This is caused by the inactivation of sodium-potassium adenosine triphosphatase (ATPase) and alterations in the expression of cell membrane channel genes (Miller et al., 1979). The interaction between GCs and proteins can render proteins unstable and susceptible to oxidation in the eyes (Bucala et al.,1985; Harris and Gruber, 1962).

Besides, GCs suppress defensive antioxidant elements such as ascorbic acid and glutathione in lens cells (Jobling and Augusteyn, 2002; Harris and Gruber, 1962). They also interfere with the proliferation and differentiation of lens epithelial cells into fiber cells, promoting the survival of epithelial cells via the dysregulation of various growth factors and cell adhesion molecules in the eye (James, 2007). Proliferated and undifferentiated epithelial cells begin to migrate and settle in the posterior part of the lens, forming large cell masses, which contributes to the development of cataracts (Jobling and Augusteyn, 2002).

Another possible cataractogenic mechanism of GCs is an augmentation in glucose concentration within lens cells, as a result of reduced hexokinase activity and elevated glucose-6-phosphate level. (Nishigori et al., 1987). In summary, GCs disturb function and structure of lens cells through osmotic, metabolic, and oxidative alterations, ultimately leading to the development of cataracts.

A few studies have established posterior subcapsular cataracts in animal models since it occurs after a prolonged period of GC treatment. For example, the injection of betamethasone (2 mg/day subconjunctivally) in albino rabbits resulted in cataract signs after 41 weeks, which was associated with a diabetic condition starting from week (Tarkkanen et al., 1966). In the study of Wood et al. (1967) opacity in the subcapsular lens layer in New Zealand white rabbits was induced after 4-6 months of topical administration of corticosteroids three times a day .

However, Bucala et al. (1985) intravitrealy injected dexamethasone, prednisolone, and cortisol at doses ranging from 20-200 nmol/0.2 mL in rabbitsand reported posterior sub-capsular alterations after 8 days, especially with a high dose of prednisolone.

Brown Norway rats receiving both topical prednisolone solution and i.v. pulses (10 mg/kg/day) showed anterior and posterior cataracts after 10 months (Nagai et al., 2004). Cataracts can also occur in fetuses of rabbits, rats, mice and chickens when GCs are administrated before birth (Buchman, 2001). Moreover, culturing chick embryos in the presence of different GCs, such as dexamethasone, hydrocortisone and prednisolone, resulted in opacities of lens (Kosano H, Nishigori, 2002).

The main limitation of GC-induced cataracts is the need for prolonged administration of GCs, which may be associated with other adverse effects.

Conclusion

In conclusion, GCs, commonly used in the treatment of various inflammatory diseases, come with a range of side effects these complications vary depending on the patient's risk factors, age, gender, and the dosage of GCs administered. Animal models can help us rationally prescribe GCs, provide appropriate treatment regimens, and prevent unwanted side reactions. These models offer insights into the potential mechanisms of GC actions, guiding the development of GC synthesis methods and effective therapeutic strategies to address these complications. It is necessary to design several animal models to gain a comprehensive understanding of the functional mechanisms of GCs. Induction of some complications such as pseudo cerebral tumor (Newton and Cooper, 1994), pancreatitis (Levine and McGuire, 1988), psychosis (Naber et al., 1996) and other clinically reported adverse effects of GCs should be performed

in a variety of animal models to explain the full effects of GCs and ways to prevent unwanted outcomes.

Conflict of interest

The authors declare that there is no conflict of interests.

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