ABSTRACT. Adrenal glucocorticoids (Gc) are among the most significant hormones in the mammalian organisms; these steroids may reach and penetrate all tissues where they interact with cytoplasmic/nuclear receptors, through which they exert multiple and very multifaceted actions. The effects of physiological concentrations of Gc on brain functions have not been completely clarified, even though Gc are recognized to influence behavioral responses, emotions, cognitive processes and to take part in the neuroendocrine control of body homeostasis. Developmental programming effects of Gc in animal models and humans have been proposed. Actually, pre-natal stress, or exposure to high Gc levels, would somehow affect neuronal developmental events in some structure and this can lead to central nervous system altered functions, as the impairment of neuroendocrine activities, cognitive processes, sleep and mood disorders. Interestingly, it has been observed that these abnormalities may not be limited to the first directly exposed individuals but transmissible across generations. The establishment of animal models with localized pre-natal glucocorticoid receptors deficiency led to the accumulation of data on the possible roles of these hormones on development of the central and peripheral nervous system. The most recent findings on the effects of Gc on neuroblast development, with particular attention to neuronal migration, will be presented.

INTRODUCTION
Glucocorticoid hormones (Gc), known also as ‘corticosteroids’, are 21-carbon steroids secreted by the adrenal cortex together with mineralocorticoids (Mc) and androgens. Gc are among the most prevalent hormones in the mammalian organisms; these steroids reach all tissues, including the brain, readily penetrate the cell membranes and interact with ubiquitous cytoplasmic/nuclear receptors, through which they exert many and very diversified actions. Cortisol is the major biologically active natural Gc in humans; the main Gc in rodents is represented by corticosterone which exerts both glucocorticoid and mineralocorticoid activities (Fig. 1).

Production and release of Gc by the adrenal gland is tightly regulated by the ACTH, secreted from the anterior pituitary gland in response to both vasopressin and hypothalamic CRH, giving origin to the hypothalamic-pituitary-adrenal axis (HPA).

The whole range of actions of Mc and Gc are mediated by binding to two distinct intracellular transcription factors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), respectively. The MR and GR bind to DNA at hormone-responsive elements comprised of two hexanucleotide half-sites, recruiting coactivator or corepressor complexes containing histone-modifying enzymes (1). The histone modifications promote an open or closed chromatin environment, thereby influencing the rate of transcription (2).

Upon binding to GR, Gc act on a variety of cell types by regulating the transcription of specific target genes. This, in turn, leads to the display of their main actions, like the maintenance of homeostasis under basal and stressful conditions, the modulation of the intermediate metabolism by the mobilization of energy resources (hepatocytes and adipocytes), the control of the immune system and the regulation of body adaptive responses to stress by the integration of permissive, suppressive, and stimulatory effects (3).

Gc protect the body from an excessive response to stressful events and, conversely, emotional or physical stress stimulates Gc secretion, by activating the HPA axis. Since stress responses and the general adaptation syndrome were first described by Hans Selye in 1936 (4), there has been an exponential increase of scientific discoveries involving the Gc, the endpoint of the “stress hormone cascade” in the body. Chronically elevated Gc levels lead however to severe pathological consequences, as it happens in patients with Cushing’s syndrome.

Gc are not only involved in adult physiology, but also in developmental processes, like lung maturation, chromaffin cell differentiation and erythroblast proliferation (5-7). In mice, GR are expressed in most fetal tissues, including placenta (8), and GR deletions lead to animal death during the first minutes after birth due to lungs atelectasis and anomalies present in other organs (9) suggesting a role of Gc in tissue maturation and differentiation. In humans, GR have been detected in many fetal neurons.
tissues beginning from 8 to 10 weeks of gestation (10) and pre-natal Gc exposure may be associated with a re-
duction in birth weight (11).
A developmental programming effects of Gc has been re-
cently reviewed (9); interestingly, a number of genes in-
volved in the Gc pathway has been shown, also in hu-
mans, to be regulated by epigenetic modifications as a con-
sequence of early life adversities. Ultimately, an in-
creasing number of evidences indicate that Gc pro-
gramming effects may not be limited to the first directly
exposed individuals but may be transmissible across gen-
erations; for instance, alterations in Gc-induced DNA
methylation have been observed up to the second gen-
eration following hormonal exposure (12).

**EFFECTS OF GC ON ADULT BRAIN FUNCTIONS**

It is accepted that Gc may influence behavioral respons-
es, emotions, cognitive processes like learning and mem-
ory, induce anxiety, and participate in the neuroen-
docrine control (13, 14). GR and MR are expressed in spe-
cific areas of the brain, with a higher density within the
limbic system; however, the effects of physiological con-
centrations of Gc on the brain have not been complete-
lly unraveled.

Gc, or their synthetic analogs, have been widely used in
the last 50 yr as pharmacological agents in a variety of
human diseases for the treatment of inflammatory syn-
dromes (i.e., asthma and allergic diseases), autoimmune
diseases as well as many other illnesses for which these
steroids are considered the medication of choice. Nev-
evertheless, Gc may produce serious adverse side effects,
including several types of alterations of central nervous
system (CNS) functions; occasionally, these collateral ef-
facts have provided indirect indications on the possible
physiological actions of Gc (3). Chronically elevated lev-
eels of circulating Gc appear to impair brain functions and
lead to the occurrence of pathological conditions like la-
tent or overt mood and sleep disorders, memory deficits
and depressive illnesses, which may occasionally result
in suicidal behavior (3).

Gc treatment may affect many physiological pro-
cesses in the brain such as neurogenesis and synaptic plasticity,
and may induce physical damage of some brain Gc-re-
sponsive regions. In primates, either stress or high Gc ex-
posure can alter hippocampal structures, damaging
memory and behavior (15). At the level of the hip-
pocampus, Gc may facilitate or impair the functions of
this structure by influencing cell survival, dendritic re-
modeling, and synaptic transmission (16), whose molec-
ular mechanism are yet to be characterized. The recent
discovery of a possible modulatory effect of Gc on adult
neurogenesis in the ethiology of depression (17) as well
as a direct effect of Gc on the induction of the thyroid
hormone-dependent Kruppel-like Factor 9 gene, a tran-
scription factor implicated in post-natal neuronal devel-
opment and plasticity, at the level of hippocampal neu-
rons (18, 19) open new perspectives in our understanding
of the Gc action on brain functions.

Gc effects on the CNS are mediated mainly by GR and
MR, and a better, but still incomplete, definition of the
biological functions of receptor activation has been ob-
tained by the specific deletion of GR at defined times of
postnatal age (conditional GR mutagenesis) (20). Addi-
tional information on positive/negative Gc actions on the
developing brain became recently available by the study
of the occurrence of metabolic abnormalities in the off-
spring consequent to the antenatal treatment with the
synthetic Gc dexamethasone (DEX), to promote lung de-
velopment, as well as by altered neuroendocrine func-
tions and behavior observed in the adult, after the ex-
posure to excess Gc during critical stages of fetal brain
development (21, 22).

At the cellular level, ligand-activated GR was found to
impair proliferation and differentiation of neuronal pro-
genitor cells in vivo and in vitro (23). The GR inhibitory
functions on growth of undifferentiated cells in embry-
onic brain, seem to be modulated by intermediate fila-
ments composed of nestin (a marker of embryonic and
neuronal stem cells) and vimentin, which promote the cy-
toplasmic anchoring of GR impeding their nuclear translo-
cation (24). Therefore, Gc might play an important role
in programming normal brain development by their im-
plification in neuronal maturation and survival (25).

**GC IN THE DEVELOPMENT
OF PERIPHERAL NERVOUS SYSTEM**

The peripheral nervous system primarily develops from
the embryonic neural crest cells, which may undergo dif-
ferrntiation into sympatho-adrenal precursors (SA). Fur-
ther differentiation of SA cells may proceed mainly to-
wards either sympathetic neurons or adrenal neuroen-
docrine cells populating the adrenal medulla, as well as