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Corticosteroid Hormones: Endocrine Messengers in the Brain

Marian Joëls and E. Ronald de Kloet

Adrenal corticosteroid hormones reach many organs including the brain where they exert persistent actions on neuronal excitability. Normally, steroid actions will maintain the integrity of neuronal networks, yet chronically decreased or enhanced corticosteroid levels can disrupt networks and enhance susceptibility to neurodegeneration.

Corticosteroid hormones (corticosterone in rats and cortisol in humans) are produced in the adrenal gland, particularly in periods of stress (5, 12). Via the circulation, the hormones reach many peripheral organs such as the heart, liver, colon, and part of the immune system. In general, the hormones enhance the availability of glucose in the blood by inhibiting cellular glucose uptake and by affecting gluconeogenesis in liver. They have profound immunosuppressive actions and promote anti-inflammatory processes. Because of these actions on peripheral organs and the immune system, corticosteroid hormones are widely used in the clinic.

Due to their lipophilic nature, corticosteroid hormones easily pass the blood-brain barrier (see Fig. 1). In the 1950s, it was recognized that actions of the steroids at the level of the hypothalamus, in addition to the pituitary, are part of a neuroendocrine feedback loop, through which the steroids control their own secretion (5).

In the late 1960s, McEwen et al. (11) showed that, within the brain, corticosteroids are highly retained in the hippocampus. This central retention raised a number of questions: Do corticosteroid hormones affect the propagation and integration of electrical signals? If so, what are the consequences for the excitability in local networks and for the brain functions in which

these networks participate? Also, what is the role of steroids in the etiology of brain disorders? Although these issues are far from resolved, recent advances in our knowledge of the steroid receptors and their mechanism of action have helped to understand the role of corticosteroids in brain function.

Features of steroid action in the brain

From the start it was clear that the role of corticosteroid hormones in brain function is essentially different from that of “classical” neurotransmitters. This is related to their distributional network and the time span in which they work.

First, classical neurotransmitters and neuropeptides are produced within the brain and either axonally transported to the site of release or presynaptically enriched by local synthesis or uptake. This distributional network ensures a neuroanatomically defined specificity of transmitter-mediated messages to their postsynaptic target.

In contrast, steroid hormones are uniformly distributed in the brain and, as true endocrine messengers, only retained at those sites where steroid receptors are present. This holds not only for steroid hormones that are produced in the adrenal gland, but also for a recently described class of brain-born steroids: the neurosteroids (2); these neurosteroids, e.g., pregnenolone and dehydroepiandrosterone, are synthesized from cholesterol in certain brain cells.

Second, classical transmitters bind to mem-

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FIGURE 1. The adrenal hormone corticosterone (CORT) binds to receptors in hypothalamus (Hy) and pituitary (P), which results, through depression of adrenocorticotrophic hormone (ACTH) release, in downregulation of corticosteroid production (*left*). In addition, corticosterone binds to receptors in suprahypothalamic brain regions, particularly in the hippocampus (Hi). A cross-sectional representation of hippocampal formation (*right*) shows that mineralocorticoid (MR, $\blacktriangle$) and glucocorticoid receptors (GR, $\bullet$) are differentially expressed in hippocampal subfields. Number of symbols is indicative of density of receptors; size of symbol reflects degree of occupation. Neurons in CA1 area and dentate gyrus (DG) contain both receptor types. Neurons in CA3 area express mainly MR. Degree of occupation of the 2 receptor types may vary, depending on circulating steroid levels. Low corticosteroid levels ($\sim 1 \mu\text{g}/100 \text{ ml}$ plasma), as seen at the trough of the circadian release pattern (around start of inactive period), occupy MR for $\sim 70\%$, while GR are occupied for only $\sim 20\%$. With corticosteroid levels as seen at the peak of circadian cycle (and after stress; $30\text{--}50 \mu\text{g}/100 \text{ ml}$ plasma), both receptor types are almost fully occupied.

"Binding of hormone receptor dimers to the responsive elements results in changes of gene transcription . . ."

brane receptors that activate an ion conductance either directly through a channel intrinsic to the receptor complex or indirectly through modulation of second messenger activity. The former mechanism takes place within milliseconds and the latter in the range of seconds to minutes. Steroid receptors are localized in the cytoplasm or nucleus. On binding of the steroid to its receptor, the steroid-receptor complex is activated and exhibits an enhanced affinity to certain sequences of the genomic material: the hormone-responsive elements.

Binding of hormone receptor dimers to the responsive elements results in changes of gene transcription, leading to altered protein synthesis within the cell (3). These proteins in turn may be involved in membrane characteristics that are essential for the neuronal excitability (see below). Due to this genomic mechanism of action, steroid effects mediated by intracellular receptors will be slow in onset (hours) and of prolonged duration (hours to days). The steroids thus supply the possibility of a delayed neuronal reaction to environmental challenges.

Receptors

During the last decade, much information has been obtained about the structure and properties of the receptors for corticosteroid hormones. With the use of radioactively labeled ligands, it was observed that corticosterone (cortisol) can

bind to two receptor types in the brain (for review, see Ref. 6). The first type is the mineralocorticoid receptor (MR or type I); *in vitro*, this receptor displays high affinity for the natural mineralocorticoid aldosterone and also for corticosterone (dissociation constant $\sim 0.5 \text{ nM}$). The second type is the glucocorticoid receptor (GR or type II), which has a 10-fold lower affinity for corticosterone and very low affinity for aldosterone. The GR, however, effectively binds synthetic glucocorticoids such as dexamethasone. Subsequently, the brain MR and GR were cloned, and their primary structure was resolved (1). The structure turned out to be identical to the MR and GR in peripheral organs such as the kidney and liver.

Notwithstanding this similarity, phenotypical differences between MRs or GRs in brain and periphery exist. A well-documented example concerns the fact that most of the MRs in the brain bind corticosterone and aldosterone equally well, so that due to the 100- to 1,000-fold excess of corticosterone they will be generally occupied by corticosterone rather than aldosterone.

Yet, despite the difference in the prevalence of corticosterone and aldosterone, MRs in the kidney are selectively occupied by aldosterone. The difference can be explained by the colocalization in renal collecting tubules of MRs and a corticosterone-converting enzyme, 11β -hydroxy-

FIGURE 2. Corticosteroid hormones (▼) pass the cell membrane and bind to intracellular mineralocorticoid and glucocorticoid receptors (MR and GR, respectively). Activated steroid-receptor complex binds to DNA and acts as a transcription factor on genome. This results in an altered mRNA expression and, thus, protein synthesis. These proteins can affect (among other things) 1) characteristics of ion currents through voltage-gated channels, e.g., for calcium (I_{Ca}) or potassium (I_K and $I_{K(Ca)}$); 2) responsiveness to transmitters acting via ionotropic (R_I) or G protein-coupled (R_G) receptors; or 3) function of ion transporters.

steroid dehydrogenase. The high biological activity of this enzyme in the kidney, but not in most brain cells, results in the breakdown of corticosterone to a metabolite with much lower binding affinity so that aldosterone can selectively occupy the MR (7).

The MRs in the brain are not uniformly distributed (6). They are enriched in limbic structures, e.g., the hippocampus and septal area, and motor nuclei in the brain stem. GRs are more ubiquitous. Nevertheless, some nuclei such as the paraventricular nucleus in the hypothalamus and the hippocampus have a particularly high density of GRs.

Neurons in the CA1 area and dentate gyrus of the hippocampal formation display high expression levels of both MRs and GRs (Fig. 1). Due to the differential affinity of the two receptor types for corticosterone, the occupation of MRs relative to GRs in these cells will largely depend on the circulating levels of the hormone (6). Low levels of corticosteroid hormone result in ~70% occupation of MRs, whereas GRs are far less (10–20%) activated. These steroid levels occur at rest, at the start of the inactive period, that is, in the evening for humans and in the morning for rats.

High corticosteroid levels, as seen around the beginning of the active period, but particularly after stress, will occupy the GRs additionally to the MRs. Consequently, under physiological conditions, the relative MR/GR activation will shift between predominant MR activation on the one hand and concurrent MR/GR activation on the other. Pathological conditions may be associated with changes in circulating steroid levels or in the MR/GR balance in the brain, potentially

leading to insufficient MR activation or to chronic activation of both MRs and GRs.

Cellular effects

The MR- and GR-mediated effects on gene transcription are expected to alter the mRNA expression and protein synthesis of brain cells (Fig. 2). Some of these proteins may contribute to the electrical properties of the cell membrane. Possible targets for the proteins are 1) the voltage-(in)dependent ion channels in the membrane; 2) transmitter systems, comprising either ligand-gated ion channels or G protein-coupled receptors; and 3) ion transporters. For some of these putative steroid actions, evidence has been recently provided.

It is important to realize that a focused investigation of MR- and GR-mediated actions on membrane properties became possible only when selective MR and GR ligands were available, in particular, MR and GR antagonists such as RU-28318 and RU-38486, respectively. Another important factor for the recent advances was the ability to study steroid actions under voltage clamp, which can be best achieved in vitro.

Of the voltage-dependent ionic conductances examined in CA1 hippocampal cells, calcium currents appeared to be very sensitive to corticosteroid treatment (reviews in Refs. 9, 10; see Fig. 3). With predominant MR occupation, low- and high-threshold calcium currents are small. Additional GR activation results in large currents. Associated with the steroid-induced changes in calcium influx, alterations in calcium-dependent conductances were expected.

"Neurons in the CA1 area and dentate gyrus of the hippocampal formation display high expression levels of both MRs and GRs . . ."

FIGURE 3. Ionic conductances and transmitter responses in CA1 hippocampal neurons depend on corticosteroid concentration. Glutamatergic (GLU) input mediated by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPA-R), γ -aminobutyric acid (GABA)ergic input mediated by the GABA_A and GABA_B receptors, and Ca influx through voltage-gated Ca channels are shown. Low levels of corticosterone (*top left*) result in a steady AMPA- and GABA_A- and GABA_B-R-mediated synaptic flow. Voltage-gated Ca current is small. With increasing steroid levels (*top right*), AMPA- and GABA_B-R-mediated responses are reduced. Ca currents are relatively large. More extreme variations in circulating steroid levels, such as may occur during chronic hypo- or hypercorticism, severely affect neuronal excitability. In the absence of steroids, Ca currents increase. AMPA- and GABA_B-R-mediated responses are reduced, particularly with persistent stimulation of afferents. Chronic overexposure to corticosterone results in a combination of reduced GABAergic inhibition and relatively large Ca influx. Both conditions are potentially dangerous and may increase susceptibility of CA1 neurons to neurodegeneration when combined with demanding conditions such as ischemia and epilepsy.

"Transmitter responses mediated by G protein-coupled receptors are also subject to steroid modulation."

This was indeed found to be true for the calcium-dependent potassium conductance. Voltage-dependent potassium conductances are far less modulated by corticosteroids.

Synaptic responses of CA1 pyramidal neurons mediated by glutamate and γ -aminobutyric acid are maintained or enhanced with predominant occupation of MRs. The responses are stable under these conditions, even with persistent synaptic stimulation. When GRs are occupied additionally to MRs, responses mediated by the excitatory (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and inhibitory amino acid receptors decline. This is particularly evident when the synaptic afferents are repeatedly stimulated. Steroid effects on other ligand-gated ion channels, e.g., the nicotinic acetylcholine receptor, the *N*-methyl-D-aspartate, or the serotonin (5-HT)₃ receptors, have not yet been examined.

Transmitter responses mediated by G protein-coupled receptors are also subject to steroid modulation. Responses mediated by the 5-HT_{1a} or muscarinic acetylcholine receptors were found to be small with predominant MR occu-

pation, whereas additional GR occupation leads to large responses. However, responses mediated by the β_1 -adrenoceptor are suppressed by GR activation.

The above-mentioned steroid actions on intrinsic membrane properties and transmitter responses of hippocampal neurons generally developed with a delay of at least 1 h; they persisted for hours. Protein synthesis inhibitors could prevent the steroid-induced effects in all cases where they were tested.

We therefore assume that the coordinated MR- and GR-mediated control of hippocampal excitability is indeed accomplished via a genomic mechanism of action. This implies that, under physiological conditions, there will be a slow but persistent gene-mediated control of neuronal activity by the endocrine messengers.

In the hippocampal CA1 area, MRs appear to be important for sustaining the mainstream of information carried by amino acid transmitters. Notwithstanding the relatively high neuronal firing level under conditions of predominant MR occupation, the integrity of the neuronal circuit seems to be guaranteed, since local inhibition is

maintained and neuronal depolarization is associated with little calcium influx. When corticosteroid levels rise during the day or after stress, GRs will become occupied in addition to MRs. The GR-mediated effects on excitatory input, on the calcium-dependent potassium conductance, and on aminergic responses may help to suppress (temporarily raised) excitability.

So far, the features of steroid control over neuronal activity are based on observations in hippocampal CA1 neurons, which express both receptor types. It is presently unclear whether GR-mediated effects will develop likewise in neurons that do not express MRs (or the reverse). This is particularly interesting for GR-enriched neurons in the paraventricular nucleus of the hypothalamus, which are involved in the neuroendocrine feedback loop.

Too little, too much

The above-described modulation of neuronal excitability by steroids illustrates the variation that may occur with physiological fluctuations of MR and GR occupation. However, the variation in MR/GR occupation may become more extreme, e.g., with chronic hypo- or hypercorticism resulting from changes in adrenal secretion or from altered steroid receptor properties. How is neuronal activity affected by these pathological shifts in MR and GR occupation?

Studies performed in adrenalectomized rats may give an impression of what happens when corticosteroid levels are reduced to an extent that MRs (and GRs) are no longer activated. Under these circumstances, hippocampal neurons fail to respond to (particularly) the synaptic input carried by inhibitory amino acids when extensive stimulation of the afferents is applied (review in Ref. 9).

Modulatory responses induced by 5-HT, acetylcholine, and norepinephrine are relatively large. A striking feature that becomes evident 3–4 days after adrenalectomy is an enhancement of the low-threshold calcium current. The combination of failing inhibitory input with increased calcium influx could potentially increase the susceptibility to neurodegenerative processes. This has indeed been observed for neurons in the dentate gyrus, although not for other hippocampal cells (8, 14, 15).

When neurons are chronically overexposed to corticosteroids, the temporary “defense mechanisms” induced by GR activation, such as the enhancement of calcium-dependent potassium currents and the reduction of excitatory input, may no longer suffice to protect against more dangerous effects: the increased calcium cur-

rents and the reduction of inhibitory input. Also, chronic exposure to high corticosteroid levels probably implicates the energy supply to neurons (14). The combination of chronically elevated steroid levels and additional challenges to the system, such as prolonged depolarizations (cf. epilepsy) or disturbances in the energy balance (cf. ischemia), may become a serious threat for cell survival. This has indeed been observed, particularly for CA3 hippocampal cells (8, 14).

Apparently, chronic under- and overexposure to corticosteroids has profound repercussions for neuronal networks and ultimately for cell survival. What remains unclear is why some neurons (i.e., in the dentate gyrus) are so sensitive to steroid depletion and others (CA3 neurons) sensitive to steroid overexposure, while CA1 neurons are quite resistant to such extreme conditions. Only part of this differential sensitivity can be explained by local variation in expression levels for MRs and GRs.

Clearly, other factors add to the cell specificity. These factors include the local release pattern of excitatory and inhibitory amino acids and the postsynaptic localization of their receptors, intrinsic cell properties such as the dendritic morphology and cell size, the relative distribution of calcium and potassium channels over the cell surface, cellular calcium buffering and extrusion mechanisms, and, potentially, cell-specific expression of genes involved in neurodegeneration.

Functional implications

What is the physiological relevance of these cellular actions exerted by endocrine messengers in the brain? First of all, corticosteroids are secreted in the adrenal gland particularly in response to environmental challenges. Because they freely enter the brain, corticosteroids introduce a peripheral response of the body into the brain. Second, in one of the prime target areas, the hippocampus, steroids exert a long-term control over local excitability, via a coordinated MR- and GR-dependent mechanism. The steroid-mediated control of hippocampal excitability is also reflected in higher brain functions for which the hippocampal circuits are essential.

For instance, MR and GR activation were found to be important for response selection and storage of spatial information, respectively, in a rat water maze paradigm (8). Thus cellular actions via MRs and GRs in the hippocampal formation may contribute to steroid modulation of cognitive functions during stress.

Simplified as this picture may be for the

“Apparently, chronic under- and overexposure to corticosteroids has profound repercussions for neuronal networks . . .”

"average" physiological conditions, it certainly does not cover conditions in which the circulating levels of hormone are chronically altered and/or when the prevalence of MRs and GRs in the brain is changed. Even during a normal life cycle these changing conditions occur. During early postnatal development, the expression of MRs and in particular GRs in the brain is much reduced when compared with the adult state (13). In addition, this period is characterized by low adrenocortical activity. In aged animals, adrenal dysfunction is often observed. In the brain, the expression of MRs and GRs in hippocampus is diminished (10).

There are also many examples of conditions that are associated with chronic hypo- or hypercorticism, either primary (altered corticosteroid levels) or secondary, due to corticosteroid receptor defects (4). Chronic fatigue syndrome, posttraumatic stress disorder, obesity, and fibromyalgia are well-documented examples of disorders associated with hypocorticism.

Chronic hypercorticism will occur during corticosteroid therapy for treatment of inflammatory diseases and for immune suppression. In addition, chronic stress, anorexia nervosa and malnutrition, excessive exercise, and melancholic depression are associated with chronic hypercorticism. Whether these disorders, via the altered steroid secretion, affect neuronal activity and cognitive brain function and contribute to neurodegeneration is an important issue for present and future research.

"In aged animals, adrenal dysfunction is often observed. In the brain, the expression of MRs and GRs in hippocampus is diminished ..."

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