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Glucocorticoids act on glutamatergic pathways to affect memory processes

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Glucocorticoids can acutely affect memory processes, with both facilitating and impairing effects having been described. Recent work has revealed that glucocorticoids may affect learning and memory processes by interacting with glutamatergic mechanisms. In this opinion article I describe different glutamatergic pathways that glucocorticoids can affect to modulate memory processes. Furthermore, glucocorticoid–glutamatergic interactions during information processing are proposed as a potential model to explain many of the diverse actions of glucocorticoids on cognition. The model suggests that direct modulation of glutamatergic pathways by glucocorticoids could serve as an important mechanism for these hormones to directly alter cognitive functions.

Introduction

Intensive research in the last decades has uncovered stress as a major regulator of cognitive function. Glucocorticoids are steroid hormones produced by the adrenal glands whose secretion increases under stress [1]. Owing to their lipophilic nature, glucocorticoids can cross the blood–brain barrier to access to the brain where, through binding to specific receptors [mineralocorticoid (MR) and glucocorticoid (GR) receptors] and by means of slow genomic and rapid non-genomic actions, they can have multiple effects on neural function and cognition (Box 1).

Acute and chronic actions of glucocorticoids on memory processes differ in many respects, including differences in behavioral outcomes as well as in the cellular and molecular mechanisms involved. This opinion article focuses on the acute actions of glucocorticoids on memory processes including learning, consolidation, retrieval and extinction (Glossary); [2,3] for reviews on chronic effects). A key feature of the acute effects of glucocorticoids on memory function is that their effects can be quite divergent, with both facilitating and impairing effects [4,5]. Several influential models have accommodated such contradictory findings by classifying effects according to the characteristics of the glucocorticoid response and/or the memory process under study [4–12] (Box 2).

The question arises as to whether a mechanistic explanation can be provided to explain how glucocorticoids produce such a diversity of actions. Given that until recently glucocorticoids were thought to act exclusively via genomic mechanisms, research has focused predominantly on changes in gene and protein expression in response to glucocorticoids [13–16]. Because genomic mechanisms take some time to develop, such a mechanism cannot apply to extremely rapid effects of glucocorticoids reported for some cognitive operations (for example, learning and retrieval when tests are given shortly after the enhancement of glucocorticoid levels). Importantly, recent work has underscored the potential of glucocorticoids to affect memory processes and synaptic plasticity by interacting with glutamatergic mechanisms (Box 3) through both nongenomic and genomic pathways.

The first part of this article discusses studies that demonstrate glucocorticoid actions on specific aspects of glutamatergic pathways in the context of information processing. These actions include (i) genomic and non-genomic increases in extracellular glutamate levels that affect excitatory transmission, (ii) the activation of NMDA-type

Glossary

Consolidation: the process of storage of acquired information.
Extinction: a process that inhibits expression of former learned responses.
Fear conditioning task: a task in which animals learn, by association, that discrete or contextual cues predict aversive conditions.
Forced swim test: a test in which animals placed in an enclosed cylinder full of water learn that there is no escape and eventually develop a floating response.
Learning: the process involved in the acquisition of information.
Object location test: a task in which memory for a particular location of two objects to which rodent is exposed in a first phase is indicated by higher levels of exploration of one of the objects that is displaced at testing.
Object recognition test: a task in which rodent recognition of a familiar object is indicated by higher levels of exploration of a novel object when both objects are presented in a free choice test.
Inhibitory or passive avoidance task: a task in which animals learn to inhibit an innate response to avoid receiving an aversive stimulation (such as a footshock).
Priming: a process whereby learning circuits activated by a particular stimulation show reduced threshold for subsequent reactivation by similar stimulation in the near future.
Retrieval: the process of recall of stored information.
Spatial learning: a learning process whereby individuals learn to orientate themselves in their spatial environment by taking into account the location of distal visual cues. The water maze is a common behavioral paradigm used to assess spatial learning in rodents.
Swim-stress paradigm: a stress-induction procedure in which animals are exposed for a defined period of time (that normally varies from 2 to 15 min) to a water tank where there is no possibility of escape.
T-maze delayed alternation task: a working memory task in which animals learn to find rewards at the end of two arms in a T-maze by visiting the arm opposite to the previously visited one after being submitted to a certain delay.
Water maze: a behavioral task used to study spatial learning and memory. This task typically consists of a circular water tank in which rodents have to learn to locate a hidden submerged platform using distal visual cues to orientate themselves and navigate in their spatial environment.
Working memory: a cognitive process consisting of keeping recently acquired information 'online' and available to further cognitive operations during a brief period (from seconds to minutes).

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Box 1. Glucocorticoids, their receptors and mechanisms of action

Glucocorticoids (referred to as cortisol in humans and corticosterone in rodents) are the final products of the activated hypothalamus–pituitary–adrenal (HPA) axis. Corticosterone binds to two types of receptors, the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). Classically, both MR and GR have been identified as intracellular receptors acting as ligand-activated nuclear regulators and exerting slow-onset genomic effects through transrepression and transactivation. Intracellular MRs have a 10-fold higher affinity for corticosterone than GRs, implying that MRs are largely occupied under basal corticosterone conditions, whereas GR occupancy is increased when corticosterone levels rise.

Recently, evidence has emerged for rapid, non-genomic and transient effects of these receptors when expressed at the cell membrane in different brain areas [1] (Figure I). In the hippocampus, lower-affinity membrane-associated MRs were reported to be located presynaptically and to rapidly increase glutamate release probability upon activation [93]. In the lateral amygdala, non-nuclear-membrane GRs were demonstrated to be localized postsynaptically [17]. Membrane-bound GRs that are coupled to G-protein-coupled receptors (GPCRs) have been implicated in the rapid effects of corticosterone in feedback inhibitory actions in the hypothalamus that involve endocannabinoid signaling [25] and in the fast-inducing actions of corticosterone in medial PFC-dependent cognition [88].

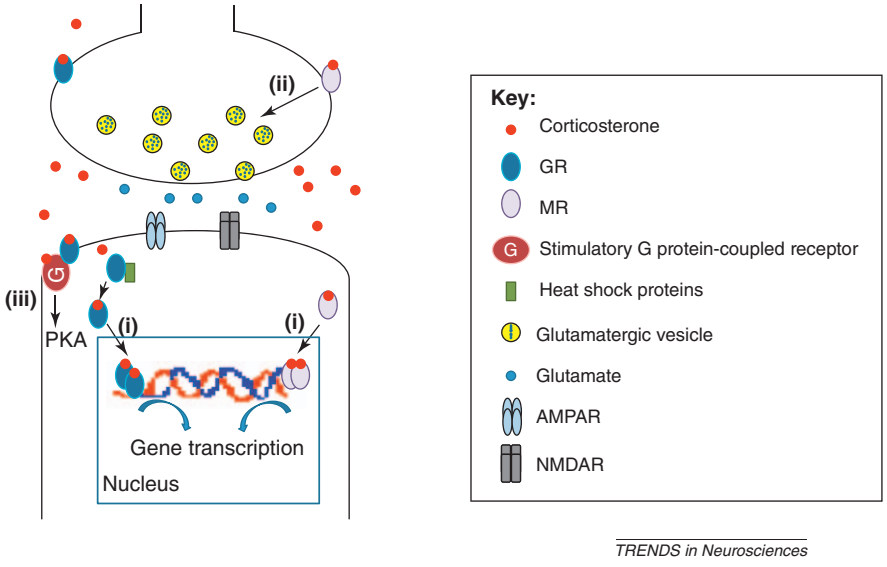

Figure I. Schematic representation of the neuronal actions of MR and GR. **(i)** Upon corticosterone binding, GRs and MRs dissociate from cytoplasmic heat shock proteins. The receptors then translocate to the nucleus where they act as ligand-activated nuclear regulators, affecting gene transcription for a large number of proteins. **(ii)** Membrane-bound MRs have been described presynaptically and have been shown to increase glutamate release. **(iii)** Membrane-bound GRs have been shown to be linked to the activation of membrane-associated GPCRs, and this results in the subsequent enhancement of cAMP signaling pathways leading to an increase in protein kinase A (PKA) activity [25].

glutamate receptors (NMDARs) and downstream signaling pathways, and (iii) increased membrane trafficking of AMPA-type glutamate receptors (AMPARs). The latter part of the article presents a model that highlights glucocorticoid–glutamatergic interactions during information processing as a key cellular mechanism that could explain many of the diverse cognitive actions of glucocorticoids.

Glucocorticoid actions on specific aspects of glutamatergic pathways

Glucocorticoids increase extracellular glutamate levels and affect excitatory transmission

One mechanism whereby glucocorticoids can affect glutamatergic pathways is by increasing extracellular glutamate levels, as described for both stress and elevated glucocorticoids in different brain areas [17]. A rise in peripheral corticosterone levels produces a rapid increase in corticosterone levels in the hippocampus in parallel with a specific increase in extracellular glutamate levels [18]. Glucocorticoid-induced increases in extracellular glutamate levels in the hippocampus can be exerted through a variety of mechanisms, including GR-mediated inhibition of glutamate uptake [19,20] and non-genomic membrane MR- or GR-mediated increase of presynaptic glutamate release probability [21–24]; nevertheless it should also be noted that a GR-mediated decrease in glutamate release probability has been observed in some brain regions such the hypothalamus [25]. However, for this mechanism to be effective it should ideally be capable of affecting excitatory transmission immediately (Figure 1a,b). This has been found to be the case in the hippocampus in connection with the primary actions of corticosterone on increased presynaptic glutamate release. The evidence includes a rapid and reversible enhancement of the frequency of miniature excitatory postsynaptic currents (mEPSCs, currents that exclusively involve AMPARs) in the hippocampal CA1 area [21] and indications of an enhanced likelihood of generating action potentials postsynaptically [1]. More recently, glucocorticoids were also found to enhance glutamatergic transmission rapidly in basolateral amygdala neurons through an MR-dependent mechanism [26]. Interestingly, in contrast to the transient effect observed in the CA1 area [21], the enhanced mEPSC activity in the amygdala is long lasting (i.e. maintained for several hours) [26], an effect that requires both rapidly induced MR-dependent [26] as well as delayed GR-dependent [27,28] enhancement of glutamatergic transmission.