Pharmacological Research 113 (2016) 1–17

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review-pharmacology across disciplines

Timing and crosstalk of glucocorticoid signaling with cytokines, neurotransmitters and growth factors

Margarita Arango-Lievano*, Freddy Jeanneteau*

Institut de Génomique Fonctionnelle, Inserm U1191, CNRS UMR5203, 34094 Montpellier, France

ARTICLE INFO

Article history:
Received 1 August 2016
Received in revised form 2 August 2016
Accepted 2 August 2016
Available online 3 August 2016

Keywords:
Glucocorticoid receptor
BDNF
Cytokines
Endocannabinoids
Neurotransmitters
Glucocorticoid resistance & hypersensitivity
Disease

ABSTRACT

Glucocorticoid actions are tailored to the organs and cells responding thanks to complex integration with ongoing signaling mediated by cytokines, hormones, neurotransmitters, and growth factors. Disruption of: (1) the amount of signaling molecules available locally; (2) the timing with other signaling pathways; (3) the post-translational modifications on glucocorticoid receptors; and (4) the receptors-interacting proteins within cellular organelles and functional compartments, can modify the sensitivity and efficacy of glucocorticoid responses with implications in physiology, diseases and treatments. Tissue sensitivity to glucocorticoids is sustained by multiple systems that do not operate in isolation. We take the example of the interplay between the glucocorticoid and brain-derived neurotrophic factor signaling pathways to deconstruct context-dependent glucocorticoid responses that play key roles in physiology, diseases and therapies.

Contents

* Corresponding authors.
E-mail addresses: Margarita.arango@igf.cnrs.fr (M. Arango-Lievano), freddy.jeanneteau@igf.cnrs.fr (F. Jeanneteau).

http://dx.doi.org/10.1016/j.phrs.2016.08.005
1043-6618/

1. Introduction

A dual receptor system senses variations of corticoid concentrations that can increase by 10–100 times during circadian and ultradian cycles and by 200 times during stress [1]. These two types of corticoid receptors are: The mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Glucocorticoids have approximately a ten-fold higher affinity for MR than for GR, [2]. GR is mostly ubiquitous unlike MR, and in the brain GR expression is widely distributed whereas MR is highest in the hippocampus [3,4]. Secretion of glucocorticoids is modulated by intrinsic factors (e.g. circadian cycles, inflammation, infection) and extrinsic cues (e.g. changing environment, exercise, learning, stress) in order to facilitate homeostasis. Failure to trigger appropriate glucocorticoid response and thus return to homeostatic state could result in deviation of cells and organs from normal physiology towards unfavorable chronic conditions [5,6]. This is why glucocorticoids are of paramount importance in metabolism, inflammation, immunity, cognition, and cardiovascular functions [7].

Synthetic glucocorticoids are primary options for the treatment of many inflammatory and immune diseases. Glucocorticoid therapy causes severe side effects that are GR-mediated [8]. Besides the undesirable effects, tolerance to glucocorticoids resulting in decreased sensitivity and efficacy is problematic as patients cannot respond any more to glucocorticoid therapy or endogenous glucocorticoids. The establishment of unfavorable states of glucocorticoid resistance or hypersensitivity is a risk factor for developing diseases associated with chronic inflammation [7]. Yet, only a subset of individuals is at risk of developing these conditions suggesting a high degree of inter-individual variability in the glucocorticoid response outcomes. This is because the functions of glucocorticoid receptors (GR and MR) vary with the age, gender, dosage, timing and context at exposure [9,10]. Based on this knowledge, the challenge for therapies is not necessarily to develop more specific ligands for GR since side effects are GR mediated, but to use glucocorticoids as mainstay of treatment with other therapies targeting the physiological context. Understanding how GR functions can change in different physiological context or between individuals becomes a priority.

Different physiological contexts result in a variety of signaling pathways activated in concomitance with GR signaling. Converging signaling pathways act in part by altering GR phosphorylation that fosters the recruitment of interacting co-regulatory molecules in the mitochondria, cytoplasm, synapse and nucleus [11,12]. As a result, GR deploys rapid non-genomic and slow genomic mechanisms together with ongoing signaling activities to promote cellular adaptation to the physiological context [13]. This review proposes a contemporary view of GR signaling in the context of interacting signaling pathways that modify GR functions with post-translational modifications or cooperate at the level of the epigenome to prime a suitable response. For reviews focusing on MR post-translational modifications and interactions with non-canonical pathways see [14].

The vast web of intracellular signaling pathways interacting with glucocorticoid receptors can modify the sensitivity and efficacy of glucocorticoid responses with implications in physiology, diseases and treatments. This review focuses on the interaction between growth factors and glucocorticoids. In particular, the relationship between the brain-derived neurotrophic factor (BDNF) and GR functions have been intensely studied in the recent years for its implication in several mental illnesses, providing a variety of results, sometimes contradicting because of the inconsistency between experimental models [15–18]. The complex interplay between BDNF and glucocorticoids on physiology and behavior can be viewed under a new perspective with recent studies evoking that BDNF provides permissive functions on GR-directed glucocorticoid responses [19,20]. This is because neuroplasticity mediated by BDNF occurs during glucocorticoid signaling in organisms responding to various internal and external cues. The molecular mechanisms underlying such interplay provide a solid framework for understanding normal and pathological glucocorticoid functions.

1.1. Glucocorticoid signaling interacts with multiple pathways

Glucocorticoids deploy rapid non-genomic and slow genomic mechanisms to exert their actions on cells, tissue homeostasis and physiology. Little is known about the mechanism of rapid glucocorticoid actions [21,22]. But previous pharmacological studies involved an elusive membrane bound glucocorticoid receptor, heterotrimeric G-proteins, cAMP and PKA [23]. This enigmatic rapid glucocorticoid pathway was further deconstructed by the identification of a necessary interaction with the endocannabinoid system, a paracrine retrograde messenger that suppresses neurotransmitter release. This system employs a G-protein coupled receptor to change intracellular levels of cAMP and promote PKA activation, thereby putting in order the pieces of this signaling puzzle: glucocorticoid – GR – endocannabinoid – CB1 – Gs-cAMP – PKA pathway [24]. On top of the rapid effects, glucocorticoids modify gene transcription to change the expression of the building blocks required for cellular adaptation. For this, glucocorticoids regulate the transcription and mRNA decay of numerous genes, as well as the translation of these RNAs [11,25–28]. The target genes of glucocorticoids are quite variable depending on cell type, circadian rhythms, age, gender, dose and duration of stimulation [25,28,29]. The number of binding sites for glucocorticoid receptors in the genome is smaller than the number of genes regulated by glucocorticoids, and the positions of these DNA ligands are often present far from the transcription start site of target genes [30]. It is yet unclear if the genes that are invariably controlled by glucocorticoids (e.g. FKBP51, CRH, GILZ. . .) benefit from glucocorticoid-responsive DNA elements in proximity of transcription start sites compared to others genes (e.g. DUSP1, NR4A1. . .) that are not systematically responding to glucocorticoid stimulation because they depend on permissive signals. The transcription of target genes by glucocorticoids requires the association of specific co-factor proteins (e.g. HSPs, FKBPs, transcription factors, SRCs, PERs. . .) that complex with GR. The abundance and activity of these co-factors may vary as a function of cell type, circadian rhythms, age, gender, dose and duration of stimulation [31,32]. Disease-specificity or tissue selectivity of some of these cofactors are currently investigated as novel therapeutic targets [33,34].

It is not only the identity of the pathways interacting with glucocorticoids but also the timing of glucocorticoid stimulation with