Inhibition of Nerve Growth Factor-Induced Neurite Outgrowth from PC12 Cells by Dexamethasone: Signaling Pathways through the Glucocorticoid Receptor and Phosphorylated Akt and ERK1/2

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Abstract
Glucocorticoids are important mediators of the stress response and are commonly employed as drugs for the suppression of immune rejection after organ transplantation. Previous investigations uncovered the possibility of mood depression in patients undergoing long-term treatment with synthetic glucocorticoids, including dexamethasone (DEX). Exogenous glucocorticoids and their synthetic derivatives can also adversely affect the development of the central nervous system. Although neurite extension from rat pheochromocytoma-derived PC12 cells and a variety of primary neurons is stimulated by nerve growth factor (NGF), and signaling pathways triggered by the binding of NGF to tyrosine kinase receptor type 1 (TrkA) function in both neurite outgrowth and neuronal survival, the effect of DEX on the activation of regulatory proteins and pathways downstream of TrkA has not been well characterized. To analyze the influence of DEX on NGF-induced neurite outgrowth and signaling, PC12 cells, a widely utilized model of neuronal differentiation, were pretreated with the glucocorticoid prior to NGF induction. NGF-induced neurite outgrowth was attenuated by pretreatment with DEX, even in the absence of DEX after the addition of NGF. Moreover, DEX suppressed the phosphorylation of Akt and extracellular-regulated kinase 1/2 (ERK1/2) in the neurite outgrowth signaling cascade initiated by NGF. Finally, the glucocorticoid receptor (GR) antagonist, RU38486, counteracted the inhibitory effect of DEX pretreatment, not only on the phosphorylation of Akt and ERK1/2, but also on neurite extension from PC12 cells. These results suggest that DEX binding to the GR impairs NGF-promoted neurite outgrowth by interfering with the activation/phosphorylation of Akt and ERK1/2. These novel findings are likely to be useful for elucidating the central nervous system depressive mechanism(s) of action of DEX and other glucocorticoids.


Editor: Ferenc Gallay Jr, University of Pecs Medical School, Hungary

Received December 18, 2013; Accepted March 3, 2014; Published March 25, 2014

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Funding: Nippon Sigmax Co., Ltd., provided support in the form of salaries for authors Y. Kojima & TW, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the author contributions section.

Competing Interests: Yoshitsugu Kojima and Takayuki Watanabe are employed by Nippon Sigmax Co., Ltd. There are no patents, products in development, or marketed products to declare. The employment of the authors does not alter their adherence to all of the policies of PLOS ONE in terms of sharing data and materials. All other authors have declared that they have no competing interests in association with this manuscript.

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Introduction
Glucocorticoids are critical mediators of the stress response in neurons and other cell types. Exposure of cells to stress triggers the glucocorticoid-mediated activation of corticotropin-releasing hormones, which in turn stimulate the synthesis of pituitary corticotropin as part of the hypothalamo-pituitary adrenal axis [1]. Glucocorticoids are also involved in cell proliferation, neurotransmitter synthesis [2], neuronal survival, and neuronal differentiation [3,4]. Clinically, synthetic glucocorticoids such as dexamethasone (DEX) are used for the suppression of immune rejection after organ transplantation and in the treatment of leukemia. However, the clinical use of synthetic glucocorticoids increases the risk of mood depression in patients receiving long-term therapy with these agents [5]. Furthermore, prenatal exposure to DEX can lead to the abnormal development of the central nervous system [6,7].

Nerve growth factor (NGF) is a member of the neurotrophin family [9] that regulates cell proliferation and differentiation within specific neural tissues during physiological as well as pathological processes [9]. In particular, NGF is essential for cognitive function, and disrupted signaling through NGF is related to the development of Alzheimer’s disease and other neurodegenerative disorders [10]. The functions of NGF are mediated by two distinct receptor types, tyrosine kinase receptor type 1 (TrkA) and the p75 neurotrophin receptor (p75NTR) [11,12]. TrkA is a high-affinity catalytic receptor for NGF, whereas p75NTR is a low-affinity non-enzymatic NGF receptor. After NGF binds to TrkA,