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Glucocorticoids, genes and brain function

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ABSTRACT

The identification of key genes in transcriptomic data constitutes a huge challenge. Our review of microarray reports revealed 88 genes whose transcription is consistently regulated by glucocorticoids (GCs), such as cortisol, corticosterone and dexamethasone, in the brain. Replicable transcriptomic data were combined with biochemical and physiological data to create an integrated view of the effects induced by GCs. The most frequently reported genes were Errfi1 and Ddit4. Their up-regulation was associated with the altered transcription of genes regulating growth factor and mTORC1 signaling (Gab1, Tsc22d3, Dusp1, Ndrg2, Ppp5c and Sesn1) and progression of the cell cycle (Ccnd1, Cdkn1a and Cables1). The GC-induced reprogramming of cell function involves changes in the mRNA level of genes responsible for the regulation of transcription (Klf9, Bcl6, Klf15, Tle3, Cxxc5, Litaf, Tle4, Jun, Sox4, Sox2, Sox9, Irf1, Sall2, Nfkbia and Id1) and the selective degradation of mRNA (Tob2). Other genes are involved in the regulation of metabolism (Gpd1, Aldoc and Pdk4), actin cytoskeleton (Myh2, Nedd9, Mical2, Rhou, Arl4d, Osbpl3, Arhgef3, Sdc4, Rdx, Wipf3, Chst1 and Hepacam), autophagy (Eva1a and Plekhf1), vesicular transport (Rhob, Ehd3, Vps37b and Scamp2), gap junctions (Gjb6), immune response (Tiparp, Mertk, Lyve1 and Il6r), signaling mediated by thyroid hormones (Thra and Sult1a1), calcium (Calm2), adrenaline/noradrenaline (Adcy9 and Adra1d), neuropeptide Y (Npy1r) and histamine (Hdc). GCs also affected genes involved in the synthesis of polyamines (Azin1) and taurine (Cdo1). The actions of GCs are restrained by feedback mechanisms depending on the transcription of Sgk1, Fkbp5 and Nr3c1. A side effect induced by GCs is increased production of reactive oxygen species. Available data show that the brain's response to GCs is part of an emergency mode characterized by inactivation of non-core activities, restrained inflammation, restriction of investments (growth), improved efficiency of energy production and the removal of unnecessary or malfunctioning cellular components to conserve energy and maintain nutrient supply during the stress response.

1. Introduction

Endogenous glucocorticoids (cortisol and corticosterone) play pivotal role in allostasis, which is defined as the active process of adapting to stressors to maintain homeostasis (McEwen et al., 2015), while synthetic glucocorticoids are commonly used as anti-inflammatory drugs (Ratman et al., 2013). The actions of glucocorticoids (GCs) are mediated by mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), which function as ligand-activated transcription factors (de Kloet, 2013). Mineralocorticoid receptors display a higher affinity for GCs than glucocorticoid receptors and are therefore activated by low levels of the stress hormones found in basal conditions (de Kloet, 2013). In contrast, glucocorticoid receptors are only transiently activated during periods of increased release of GCs (de Kloet, 2013). After binding the ligand, GRs and MRs translocate from the cytoplasm to the nucleus where they regulate the transcription of various genes. The actions of GRs on gene transcription depend on two mechanisms (Ratman et al., 2013). First, glucocorticoid receptors bind to glucocorticoid response elements in regulatory regions of particular target genes and directly alter their transcription. Second, GRs interact with other transcription factors and modify their transcriptional activity without coming into contact with DNA itself (Ratman et al., 2013). Additionally, GCs exert rapid nongenomic actions affecting neuronal excitability (de Kloet, 2013; Joels et al., 2012). Although GCs affect the transcription of hundreds of genes in the nervous system (Carter et al., 2012; Gray et al., 2014), recent reviews have focused on only a few target genes, such as SGK1, FKBP5 and Tsc22d3 (Gilz) (Castro-Vale et al., 2016; Cattaneo and Riva, 2016; Srinivasan and Lahiri, 2016), or on genes that are less frequently and consistently reported in transcriptomic studies (Supplementary data 1), such as CX3CL1, CX3CR1, TLR2 and TLR4 (Duque Ede and Munhoz, 2016). One of the reasons for such a situation is the fact that the sequencing of genomes has outpaced the functional characterization of genes and has far exceeded our ability to reassemble identified molecules into

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complex systems (Fletcher and Mullins, 2010). Furthermore, our understanding of transcriptomic data reported in the literature is further hindered by the inconsistent gene nomenclature that has evolved over time, the large number of false positive results and the patchy character of correctly identified changes in transcription (Stankiewicz et al., 2014, 2015). The solution to these problems is the application of a replicability criterion to results derived from different data sets to diminish the noise and to strengthen the signal (Ioannidis, 2005). Therefore, we searched the available literature for studies that used transcriptomic methods to identify genes regulated by GCs in the brain or in cell cultures derived from the central nervous system (CNS). To enable the comparison of data retrieved from different sources, we standardized gene names using probe IDs as the primary identifier. Additionally, this approach allowed us to identify transcripts with unknown function at the time of the original papers' publication. The most replicable changes in transcription were combined with data from physiological and biochemical studies to create an integrated view of the relationship between glucocorticoid-induced changes in transcription and brain function.

2. Technical aspects important for the interpretation of transcriptomic data

A previous detailed analysis of studies investigating the transcriptomic mechanisms of pain revealed that there is no single gene reported in all analyzed studies (LaCroix-Fralish et al., 2011), and a similar situation was encountered in our review of transcriptional responses to GCs. Even genes that are well known to be regulated by GCs (for example, Fkbp5, Nfkbia and Sgk1) were reported in a minority of transcriptomic studies (Fig. 1). Numerous gaps in reported data arise from the large number of false negative results inherent in microarray experiments; the usage of microarrays with a limited number of probes, especially in the past; and the changing number of known genes and the variety of procedures researchers apply to limit the number of transcripts that are used to interpret data. For example, it is common to reject genes that are not significantly enriched in known biological pathways. This approach results in the omission of genes with an unknown or poorly characterized function. Another common strategy is to restrict lists of published genes only to transcripts displaying the highest fold changes. This approach ignores the fact that some proteins involved in neuronal excitability and metabolism are so important for maintaining homeostasis that they cannot undergo large changes in cellular concentration. This means that even small changes in the transcription of these genes are important for the cell function. Furthermore, the brain contains highly specialized cells, such as various types of excitatory and inhibitory neurons, astrocytes, oligodendrocytes and microglia, as well as cells associated with brain vascular and lymphatic systems. Therefore, transcriptional responses that are restricted to subpopulations of cells are not likely to result in high fold change in the total pool of transcripts isolated from homogenized tissue. The picture that emerges from transcriptomic data is further complicated by the timing between tissue collection and the dynamics of transcription and the degradation of various transcripts. All of these technical aspects are important for interpreting published data and understanding the limitation of transcriptomic studies.

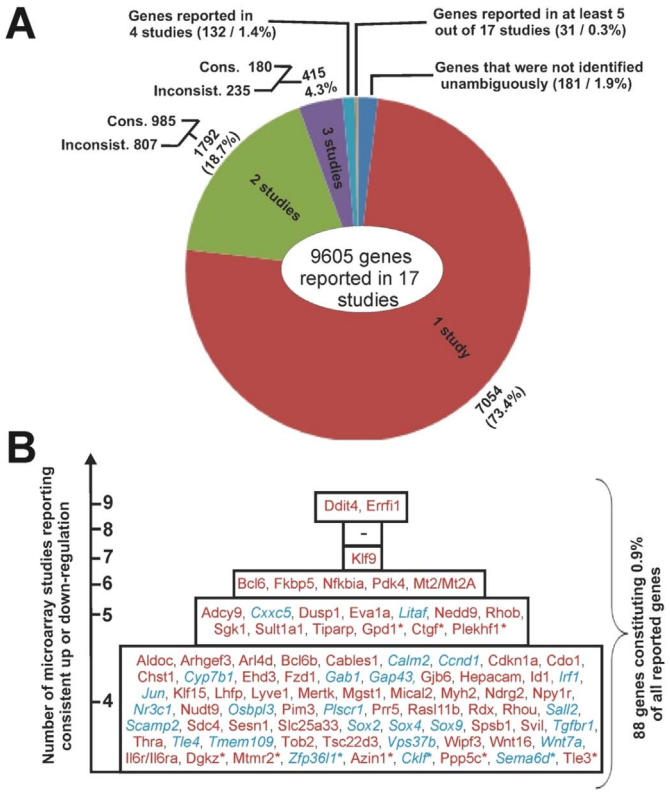

Fig. 1. Replication rate of genes reported in transcriptomic studies that investigated an effect of GCs on gene transcription in the brain or in cells derived from the central nervous system. A – all reported genes; B – genes that displayed the same direction of change in at least four reports; red – up-regulated genes, blue/italics – down-regulated genes; * – genes that displayed an opposite direction of change in one of the treatment groups (for more details, see Supplementary data 1).

3. Data collection and standardization

A search of the PubMed database revealed 17 transcriptomic studies that investigated the effects of cortisol, corticosterone or dexamethasone (synthetic glucocorticoid) on gene transcription in the brain or in cells derived from the central nervous system (Table 1). Transcriptomic data retrieved from papers and supplementary data were standardized using the bioDBnet/dbFind tool (https://biodbnet-abcc.ncifcrf.gov/db/dbFind.php). The original gene identifiers (input data) were converted into standardized gene names for the species used in the experiments. If available, Affymetrix or Illumina probe IDs were used as the input data for standardization, which allowed us to obtain the most up-to-date annotation for a given probe. If the probe ID was not available in the original data set or if the query using the probe ID as an input did not return data, the gene name was used as an input instead, followed by any other identifier that was provided by the authors of a given study. If by this point no standardized gene name was acquired, the output was obtained in one of three ways. If the Affymetrix probe ID was available, it was analyzed in the Affymetrix proprietary database (NetAffx™ Analysis Center, https://www.affymetrix.com/analysis/index.affx). In a few cases, where an ambiguous description of a gene was provided, the standardized gene name was recovered manually. Finally, if we were unable to obtain a standardized gene symbol, the original gene name was used. The obtained list of genes was sorted according to the frequency and consistency of transcriptional responses (up- or down-regulation reported in separate papers) using a proprietary R script. The resulting lists of genes were corrected in cases where the corresponding genes (orthologs) in mice, rats or humans have different names (Mt2/Mt2a and Il6r/Il6ra).

4. General characteristics of reviewed data

The analysis of transcriptomic data retrieved from the 17 studies (Table 1, Supplementary data 1) revealed 9,605 genes that were significantly regulated by GCs (Fig. 1A). Most of them were reported only in one or two papers and frequently displayed an inconsistent direction of change. Eighty-eight genes that displayed the same direction of change in at least four studies constituted 0.9% of all reported transcripts, and only two of them were reported in more than half of all analyzed papers (Fig. 1B). There was also a small group of genes (Acot1,