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Stress and trauma: BDNF control of dendritic-spine formation and regression

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ABSTRACT

Chronic restraint stress leads to increases in brain derived neurotrophic factor (BDNF) mRNA and protein in some regions of the brain, e.g. the basal lateral amygdala (BLA) but decreases in other regions such as the CA3 region of the hippocampus and dendritic spine density increases or decreases in line with these changes in BDNF. Given the powerful influence that BDNF has on dendritic spine growth, these observations suggest that the fundamental reason for the direction and extent of changes in dendritic spine density in a particular region of the brain under stress is due to the changes in BDNF there. The most likely cause of these changes is provided by the stress initiated release of steroids, which readily enter neurons and alter gene expression, for example that of BDNF. Of particular interest is how glucocorticoids and mineralocorticoids tend to have opposite effects on BDNF gene expression offering the possibility that differences in the distribution of their receptors and of their downstream effects might provide a basis for the differential transcription of the BDNF genes. Alternatively, differences in the extent of methylation and acetylation in the epigenetic control of BDNF transcription are possible in different parts of the brain following stress.

Although present evidence points to changes in BDNF transcription being the major causal agent for the changes in spine density in different parts of the brain following stress, steroids have significant effects on downstream pathways from the TrkB receptor once it is acted upon by BDNF, including those that modulate the density of dendritic spines.

Finally, although glucocorticoids play a canonical role in determining BDNF modulation of dendritic spines, recent studies have shown a role for corticotrophin releasing factor (CRF) in this regard. There is considerable improvement in the extent of changes in spine size and density in rodents with forebrain specific knockout of CRF receptor 1 (CRFR1) even when the glucocorticoid pathways are left intact. It seems then that CRF does have a role to play in determining BDNF control of dendritic spines.

Contents

Abbreviations: BDNF, brain derived neurotrophic factor; bPIX, guanine nucleotide exchange factor for RAC (GEF); CaMK2, calcium calmodulin-dependent kinase 2; CaMKK, calcium calmodulin-dependent protein kinase kinase; cofilin, severs and depolymerizes ADPactin; D2, dopamine D2 receptor; EphB, ephrin receptor; ErbB2, receptors for neuregulin; ErbB4, receptors for neuregulin; ERK, extracellular signal-regulated kinases; GKAP, guanylate kinase-associated protein; Gp, G-protein; HOMER, scaffolding protein; IP3, inositol triphosphate; kalirin, Rho GEF; LIMK, LIM kinase, phosphorylates ADF/cofilin; NMDA, N-methyl-d-aspartate; NR1, NR2A, NR2B, subunits of the NMDA receptor; NRG-1, neuregulin 1; PAK, downstream effector of RAC (sometimes called P21-activated kinase); pCREB, phosphorylated cyclic AMP response element-binding protein; PDZ, protein domain; PLCb, protein lipase Cb; plexin A, receptor for Sema 3A; PP1, protein phosphatase 1; profilin, actin regulatory molecule; PSD-95, postsynaptic density 95, a scaffolding protein; RAC, Rho-GTPase; RAS, Rho-GTPase; RhoA, Rho-GTPase; Rho-GTPase, Rho-family GTPases, a subgroup of the superfamily of GTPases; ROCK, Rho-associated kinase; sema 3A, semaphorin 3A; SFK, src family kinase; SHANK, scaffolding molecule; TrkB, BDNF receptor; WASP, Wiskott Aldrich syndrome protein that triggers actin polymerization via Arp 2/3 complex.

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1. Introduction

Chronic restraint stress leads to increases in brain derived neurotrophic factor (BDNF) mRNA and protein in some regions of the brain, e.g. the basal lateral amygdala (BLA) but decreases in other regions such as the CA3 region of the hippocampus and dendritic spine density increases or decreases in line with these changes in BDNF. Given the powerful influence that BDNF has on dendritic spine growth (see Section 4 below), these observations suggest that the fundamental reason for the direction and extent of changes in dendritic spine density in a particular region of the brain under stress is due to the changes in BDNF there. The most likely cause of these changes is provided by the stress initiated release of steroids, which readily enter neurons and alter gene expression, for example that of BDNF, as described in Section 2. Of particular interest is how glucocorticoids and mineralocorticoids tend to have opposite effects on BDNF gene expression offering the possibility that differences in the distribution of their receptors and of their downstream effects might provide a basis for the differential transcription of the BDNF genes (see Section 2.4). Alternatively, differences in the extent of methylation and acetylation in the epigenetic control of BDNF transcription are possible in different parts of the brain following stress, and this is investigated in Section 3.

Although present evidence points to changes in BDNF transcription being the major causal agent for the changes in spine density in different parts of the brain following stress, steroids have significant effects on downstream pathways from the TrkB receptor once it is acted upon by BDNF, including those that modulate the density of dendritic spines. This possibility is surveyed in Sections 4 and 5, first through a description of these downstream pathways (Section 4) and then of how they are modulated by steroids (Section 5).

Finally, although glucocorticoids play a canonical role in determining BDNF modulation of dendritic spines, recent studies have shown a role for corticotrophin releasing factor (CRF) in this regard. There is considerable improvement in the extent of changes in spine size and density in rodents with forebrain specific knockout of CRF receptor 1 (CRFR1) even when the glucocorticoid pathways are left intact (Govindarajan et al., 2006). It seems then that CRF does have a role to play in determining BDNF control of dendritic spines and this is investigated in Section 6. Finally, other receptors besides that of CRFR1 also modulate the expression of the BDNF gene, including those for cannabinoids, serotonin, and glutamate and as such their roles are also considered (in Sections 7 and 8).

This review concludes with the suggestion (see Section 9) that the core issue in disabilities related to traumatic stress arises from failure of the normal operation of various reasonably well identified neural networks as a consequence of the inappropriate regression or growth of dendritic spines that subserve these networks. It follows that the critical translational effort should be to intervene in such a way as to prevent these changes or to reconstitute the normal spine densities once the stress effects have taken place. This being the case it is of paramount importance to identify details of the mechanisms by which different steroid receptors differentially modulate BDNF gene expression.

2. BDNF gene transcription controlled by glucocorticoid and mineralocorticoid receptors

2.1. The BDNF gene

The rat BDNF gene consists of four short 5′ exons and a 3′ exon encoding the mature BDNF protein (Timmusk et al., 1993). Quantitative PCR analysis of BDNF mRNA containing these five upstream exons indicates that each of the alternative transcripts is most abundant in the hippocampus, intermediate in the substantia nigra and cerebellum and least abundant in the striatum, although the magnitude of these differences in expression varies indicating