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REVIEW

MECHANISMS UNDERLYING THE INTERACTIONS BETWEEN RAPID ESTROGENIC AND BDNF CONTROL OF SYNAPTIC CONNECTIVITY

D. P. SRIVASTAVA,[a]* K. M. WOOLFREY[b] AND P. D. EVANS[c]

[a] *Department of Neuroscience & Centre for the Cellular Basis of Behaviour, The James Black Centre, Institute of Psychiatry, King's College London, London SE5 9NU, UK*

[b] *Department of Pharmacology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO 80045, United States*

[c] *The Inositide Laboratory, The Babraham Institute, Cambridge CB22 3AT, UK*

Abstract—The effects of the steroid hormone 17β-estradiol and the neurotrophin brain-derived neurotrophic factor (BDNF) on neuronal physiology have been well investigated. Numerous studies have demonstrated that each signal can exert powerful influences on the structure and function of synapses, and specifically on dendritic spines, both within short and long time frames. Moreover, it has been suggested that BDNF is required for the long-term, or genomic, actions of 17β-estradiol on dendritic spines, via its ability to regulate the expression of neurotrophins. Here we focus on the acute, or rapid effects, of 17β-estradiol and BDNF, and their ability to activate specific signalling cascades, resulting in alterations in dendritic spine morphology. We first review recent literature describing the mechanisms by which 17β-estradiol activates these pathways, and the resulting alterations in dendritic spine number. We then describe the molecular mechanisms underlying acute modulation of dendritic spine morphology by BDNF. Finally, we consider how this new evidence may suggest that the temporal interactions of 17β-estradiol and BDNF can occur more rapidly than previously reported. Building on these new data, we propose a novel model for the interactions of this steroid and neurotrophin, whereby rapid, non-genomic 17β-estradiol and acute BDNF signal in a co-operative manner, resulting in dendritic spine formation and subsequent stabilization in support of synapse and circuit plasticity. This extended hypothesis suggests an additional mechanism by which these two signals may modulate dendritic spines in a time-specific manner.

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Key words: dendritic spines, signal transduction, oestrogen receptors, 17β-estradiol, TrkB, brain-derived neurotrophic factor.

Contents

INTRODUCTION

A defining feature of neuronal function is the capacity of neurons to adapt dynamically in response to changes in extracellular stimuli. This ability to adapt can take many forms, from changes in intrinsic excitability to modifications in the strength of synapses through the trafficking of glutamate receptors, to alterations in the shape and number of synapses. The latter form of neuronal plasticity is now recognized as an essential part of normal physiology and is posited to contribute to

*Corresponding author.
E-mail address: deepak.srivastava@kcl.ac.uk (D. P. Srivastava).

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CaMKK, calmodulin-dependent protein kinase; CP-AMPAR, calcium permeable AMPA receptors; CREB, cAMP response element-binding protein; ER, oestrogen receptor; EGFR, epidermal growth factor receptor; ERK, extracellular signal regulate; ERE, oestrogen response element; ERX, estrogen receptor X; GEF, guanine nucleotide exchange factor; GAD, glutamate decarboxylase; GFP, green fluorescent protein; GnRh, gonadotropin-releasing hormone; GPCR, G-protein-coupled receptor; GPER, G-protein-activated oestrogen receptor; HA, human influenza hemagglutinin tag; HEK, human embryonic kindney; JUNK/JUN, c-Jun N-terminal kinase; LTP, long-term potentiation; MAP, mitogen-activated protein; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, *N*-methyl-D-aspartic acid; PDZ, post synaptic protein 95, discs large and zonuula occudens protein; PELP1, proline-, glutamic acid- and leucine-rich protein-1; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; POMC, pro-opiomelanocortin; PSD, post-synaptic density; ROCK, Rho-assoicated protein kinase; TBS, theta-bust stimulation; Trk, tropomyosin-related kinase; VGCC, voltage-gated Ca^{2+} channels.

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experience-dependent learning and to the shaping of behavioural responses to different stimuli (Chklovskii et al., 2004; DeBello, 2008; Bhatt et al., 2009; Holtmaat and Svoboda, 2009). While numerous studies have focused on how activity-dependent stimuli regulate synapse morphology and number (Alvarez and Sabatini, 2007; Bhatt et al., 2009; Holtmaat and Svoboda, 2009), it is becoming increasingly clear that other extracellular stimuli can have profound effects on these structures (Waterhouse and Xu, 2009; Srivastava et al., 2011). Moreover, an emerging theme is that multiple extracellular signals may converge on the same neurons, thus achieving synergy in the molecular and cellular responses elicited by each of these signals individually (Srivastava, 2012).

The steroid hormone 17β-estradiol and the neurotrophin brain-derived neurotrophic factor (BDNF) represent two extracellular signalling molecules that have diverse effects throughout the body and within the CNS. Many of these effects are similar, or even identical, which has led to the hypothesis that these signals are co-dependent, or at least, act synergistically to affect physiology (Scharfman and Maclusky, 2005; Numakawa et al., 2010). Indeed, there is much experimental evidence that both systems interact at a number of levels, and are important for both normal and disease physiology (Scharfman and Maclusky, 2005, 2006; Sohrabji and Lewis, 2006; Numakawa et al., 2010). Many of these topics are also covered in other reviews in this Special Issue. In the past 5–10 years, our understanding of how 17β-estradiol and BDNF can modulate the structure of synapse has greatly increased. For example, it is now clear that in addition to the long-term effects of 17β-estradiol on synapses (McEwen and Alves, 1999), this hormone can also rapidly influence intracellular signalling cascades, synaptic structure and the physiology of neurons from multiple brain regions (Woolley, 2007; Srivastava et al., 2011; Srivastava, 2012). In addition, recent advances have enhanced our understanding of the molecular mechanisms of BNDF synthesis, release and actions at synapses suggesting that they can occur at multiple levels (Greenberg et al., 2009; Waterhouse and Xu, 2009). Collectively, these studies suggest that the convergence of these two signalling pathways may be more complex than originally proposed, and could involve multiple, yet distinct, mechanisms dependent on their temporal signalling characteristics.

In this review, we have concentrated on the rapid (acute) effects of both 17β-estradiol and BDNF on the regulation of synapse structure and number. First, we provide an overview of some of the advancements in our understanding of the signalling cascades activated in response to acute 17β-estradiol treatment and the identity of the oestrogen receptors (ERs) which mediate these effects. Second, we describe how BDNF and its receptors can signal in neuronal cells. We then go on to review recent studies describing how the acute effects of 17β-estradiol and BDNF can regulate synapse structure, and specifically dendritic spine morphology and number. Finally, we argue that the actions of 17β-estradiol and BDNF may be co-ordinated within a shorter time-frame than has been previously reported. This interaction may rely on the co-operation of distinct signalling systems, which ultimately result in long-lasting changes in synapse morphology and number.

SECOND MESSENGER AND SIGNALLING CASCADES INVOLVED IN TRANSDUCING RAPID ESTROGENIC SIGNALLING

Rapid estrogenic signalling has been shown to contribute to many different neuronal functions, including synaptic plasticity, cognition, neuroprotection, hyperalgesia and homoeostasis (Woolley, 2007; Brinton, 2009; Srivastava and Penzes, 2011). Recent evidence has been presented indicating that oestrogens can be rapidly produced locally within discrete regions of the brain (Cornil et al., 2006; Saldanha et al., 2011; Srivastava et al., 2011). In support of this aromatase, the key enzyme in the synthesis of 17β-estradiol has been reported to be expressed and regulated in an activity-dependent manner, in a number of brain regions (Cornil et al., 2006; Remage-Healey et al., 2011; Saldanha et al., 2011; Srivastava et al., 2011). Moreover, it has been reported that significant levels of 17β-estradiol can be detected in the hippocampus and cortex of male and female rats even following the removal of the gonads (Konkle and McCarthy, 2011). Collectively, these data have led to the suggestion that a significant portion of rapid estrogenic signalling in the brain is due to locally produced 17β-estradiol (Cornil et al., 2006; Srivastava et al., 2011). However, the receptors, second messenger pathways and signalling cascades underlying these effects in neuronal systems are not well defined and in many cases are highly controversial. Evidence has been presented for the involvement of the classical ERs – ERα and ERβ – in rapid oestrogen-mediated cell membrane events, together with the newly discovered oestrogen-activated G-protein-coupled receptor (GPCR), GPR30 (G-protein-activated ER (GPER)), and with a range of classical ion channels (Fig. 1). Importantly, signalling events may also be mediated by yet uncharacterized cell surface signalling molecules, such as ERX (estrogen receptor X), and the STX receptor. It is also possible that the different rapid effects of 17β-estradiol are mediated by different combinations of the above receptor types in different neuronal cell types (Raz et al., 2008; Spary et al., 2009; Srivastava et al., 2011; Scott et al., 2012).

A considerable amount of evidence indicates that the rapid non-genomic actions of 17β-estradiol in the nervous system, underlying both synaptic plasticity and neuroprotection, may involve the activation of multiple kinase pathways including, the MAP (mitogen-activated protein) Kinase/ERK (extracellular signal regulate) pathway, the phospholipase C (PLC) pathway, protein kinase C (PKC), PI3Kinase/Akt and protein kinase A (PKA) pathways (Srivastava et al., 2011; Scott et al., 2012). There is, however, considerable debate as to how the classical nuclear receptors ERα and ERβ could