Available online at www.sciencedirect.com
ScienceDirect
Frontiers in Neuroendocrinology 27 (2006) 376–390
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Review

Estrogen and the development and protection of nigrostriatal dopaminergic neurons: Concerted action of a multitude of signals, protective molecules, and growth factors

Markus Kipp [1], Serkan Karakaya [1], Justyna Pawlak, Gilda Araujo-Wright, Susanne Arnold, Cordian Beyer *

Institute of Neuroanatomy, University Hospital RWTH Aachen, 52074 Aachen, Germany

Available online 1 September 2006

Abstract

The nigrostriatal dopamine system comprises the dopaminergic neurons located in the ventral midbrain, their axonal connections to the forebrain, and their direct cellular target cells in the striatal complex, i.e. GABAergic neurons. The major function of the nigrostriatal dopaminergic unit is the coordination and fine tuning of motor functions at the extrapyramidal level. Numerous biologically active factors including different types of growth factors (neurotrophins, members of the TGFβ family, IGFs) and peptide/steroid hormones have been identified in the past to be implicated in the regulation of developmental aspects of this neural system. Some of these developmentally active determinants have in addition been found to play a crucial role in the mediation of neuroprotection concerning dopaminergic neurons. Estrogen was identified as such a compound interfering with embryonic neuronal differentiation and cell survival. The physiological mechanisms underlying these effects are very complex and include interactions with other developmental signals (growth factors), inflammatory processes as well as apoptotic events, but also require the activation of nonneuronal cells such as astrocytes. It appears that estrogen is assuming control over or at least influences a multitude of developmental and protective cellular mechanisms rather than taking over the part of a singular protagonist.

Keywords: Estrogen; Development; Dopamine neuron; Astroglia; Growth factors; Cytokines; Glutamate; Mitochondria

1. Introduction

After several decades of intense studies, it is now generally accepted that steroid hormones, and in particular estrogen, operate in different ways to ensure the proper development and function of the mammalian brain [15,91]. The range of estrogen action in the developing CNS is no longer confined to neuroendocrine centers and hypothalamic regions related to reproduction and the hypothalamic–hypophyseal axis. And it is no longer confined to permanent organizational effects resulting finally in the induction and maintenance of structural and functional sex differences in the brain [98,130]. Such ontogenetic estrogen effects are widespread within the vertebrate CNS and affect reproductive as well as non-reproductive brain centers and neural circuits [15]. In a similar way, estrogen is implicated in the functional regulation of brain performance and neuronal activity. Basically, there exists no brain area or neuronal system that is not affected by estrogen to a greater or lesser extent, directly or indirectly. Many efforts were undertaken in the past to pinpoint and describe effects of estrogen on the development and function of non-reproductive brain systems. This should lead to a more precise understanding of gender-specific processes of brain differentiation and -activity and, in turn, provide new information whether and how estrogen can be used as a therapeutic tool in the brain [28,47]. Altogether, these studies have clearly provided evidence that estrogen, in addition to

* Corresponding author. Fax: +49 0241 80 82472.
E-mail address: cbeyer@ukaachen.de (C. Beyer).
[1] These authors contributed equally to this work.

0091-3022/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.yfrne.2006.07.001

sexual responses, affects a variety of behaviors including emotional reaction, learning memory, cognitive performance, verbal skills, and motor activity [39,76,81,97,144].

In this paper, we will in particular focus on physiological interactions of estrogen and a distinct motor control system, i.e. the nigrostriatal dopaminergic system (Fig. 1). We will further stress the issue of developmental interactions between this steroid hormone and the dopamine system but also highlight the potential interrelationship between both later during adulthood and even during neuronal degenerative processes. It is long known that this motor system shows gender differences and appears to be regulated in a gender-specific fashion [81]. Moreover, a number of publications are concerned with the role of estrogen as a developmental signal for and a functional regulator of midbrain dopamine neurons and its striatal GABAergic target cells [7,17,58,95]. Coevally, a significant set of information suggests an additional function for estrogen as a neuroprotective agent for this neural system [38,71,121,125].

Several important observations support the view that the nigrostriatal motor system is influenced by estrogen at different levels. During the perinatal period of rat brain development, the estrogen-forming enzyme aromatase is transiently expressed from embryonic day (ED) 17 until postnatal day (PD) 10 in the ventral mesencephalon [112]. In contrast, aromatase activity in the striatum is detectable before birth at low levels but increases postnatally and persists until adulthood [79]. These data are in concordance with the presence of estrogen receptors (ER) in these particular brain areas [80,96,113]. Also notably, developmental sex differences with respect to ER-α and ER-β seems to exist during postnatal days [116]. Functional and behavioral analysis in addition reveal that estrogen interferes with different steps of dopamine transmission and dopamine-dependent behavioral performance. This includes rotational behavior, dopamine synthesis, -release, -metabolism at the presynaptic levels, and dopamine receptor density/sensitivity at the postsynaptic site [9,36,68,140].

As pointed out in the chapter before, estrogen receptors are present in dopamine neurons belonging to the nigrostriatal system as well as in dopamine target cells. The expression of ERs by itself is not meaningful with respect to the description of estrogen action at the cellular level. The complexity of cellular estrogen action reached an unexpected dimension during the past years [45,53,92]. We will give here only a short introduction into this research topic, since excellent reviews in the past years have extensively discussed this matter [22,45,53,91,92]. Estrogen action generally takes place through signaling pathways involving the canonical activation of nuclear ERs. This mechanism is implicated in the regulation of gene expression and requires direct interactions with palindromic sequences in the promoter region of target genes [6]. Additionally, nonclassical signaling (also termed nongenomic, rapid estrogen effects) involving extranuclear ERs (cytoplasmatic, plasma membrane-attached, and mitochondrial-located) plays an important role for mediating physiological estrogen effects [22,71,81,105,108,114]. Often, the activation of such alternative, non-nuclear ER-dependent pathway entails the stimulation of other intracellular signaling cascades such as the

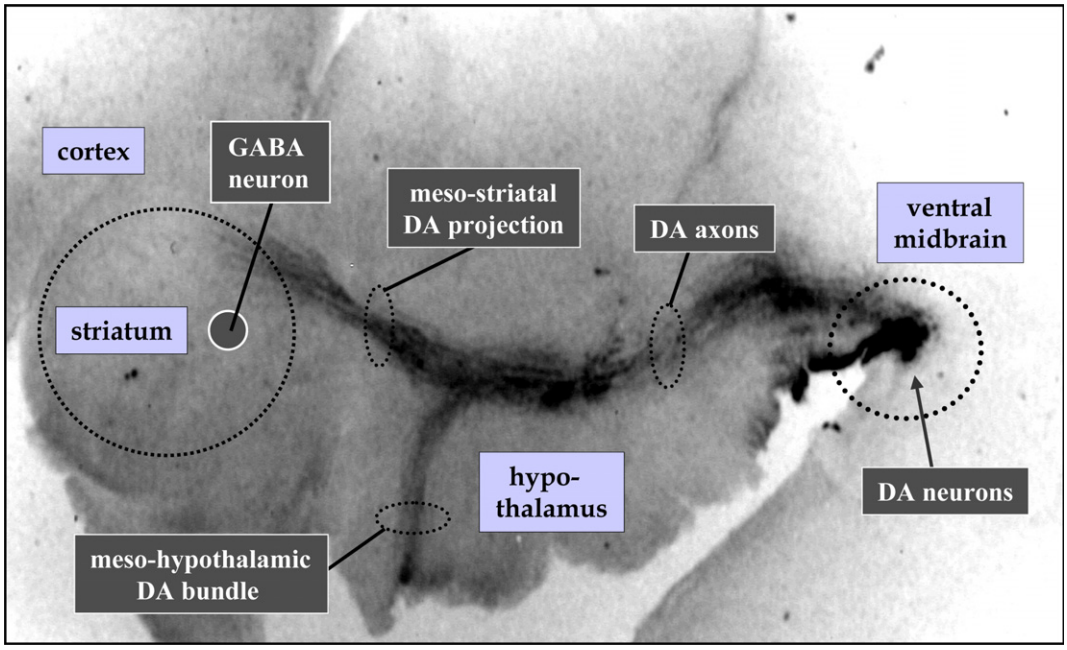

Fig. 1. Low magnification view of a parasagittal section of a late embryonic rodent brain. The section was immunocytochemically stained with an antiserum directed against the key enzyme in dopamine (DA) synthesis, thyroxin hydroxylase. Note the presence of densely packed cells (dark staining) in the ventral midbrain, i.e. DA cell groups. These neurons extend their neurites (concentrated in the median forebrain bundle, dotted circle) throughout the brain and innervate their natural target cells within the striatal complex, i.e. striatal GABAergic neurons. Not shown are the mesocortical DA projections arising from the ventral midbrain that reach cortical structures. Instead, transient meso-hypothalamic DA projections terminating in the retrochiasmatic and paraventricular region are visible (modified from Ref. [117]).