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Classical androgen receptors in non-classical sites in the brain

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Abstract

Androgen receptors are expressed in many different neuronal populations in the central nervous system where they often act as transcription factors in the cell nucleus. However, recent studies have detected androgen receptor immunoreactivity in neuronal and glial processes of the adult rat neocortex, hippocampal formation, and amygdala as well as in the telencephalon of eastern fence and green anole lizards. This review discusses previously published findings on extranuclear androgen receptors, as well as new experimental results that begin to establish a possible functional role for androgen receptors in axons within cortical regions. Electron microscopic studies have revealed that androgen receptor immunoreactive processes in the rat brain correspond to axons, dendrites and glial processes. New results show that lesions of the dorsal CA1 region by local administration of ibotenic acid reduce the density of androgen receptor immunoreactive axons in the cerebral cortex and the amygdala, suggesting that these axons may originate in the hippocampus. Androgen receptor immunoreactivity in axons is also decreased by the intracerebroventricular administration of colchicine, suggesting that androgen receptor protein is transported from the perikaryon to the axons by fast axonal transport. Androgen receptors in axons located in the cerebral cortex and amygdala and originating in the hippocampus may play an important role in the rapid behavioral effects of androgens.

Keywords: Androgen receptor; Androgen; Cerebral cortex; Hippocampus; Axons; Extranuclear steroid receptors; Rapid actions of steroids

Introduction

The most commonly studied role of steroid receptors has unquestionably been that of their participation as nuclear transcription factors, modulating gene transcription. However, in the 1970s and 1980s, parallel evidence began to emerge that steroids could act rapidly on cellular functions, independent of gene transcription (Kelly et al., 1977; Dufy et al., 1979; Nabekura et al., 1986). Among the first reports to show the rapid, non-genomic actions of steroid hormone receptors was an electrophysiological study published by Kelly et al. (1977) that demonstrated the rapid effects of estradiol on neuronal firing in the rat hypothalamus. Others went on to demonstrate that estradiol potentiates excitatory post-synaptic potentials in hippocampal neurons (Foy and Teyler, 1983; Wong and Moss, 1991, 1992), potentiates glutamate responses in the cerebellum (Smith et al., 1987, 1989), suppresses μ-opioid and $GABA_B$ receptor based hyperpolarization of arcuate neurons (Kelly et al., 1992), and potentiates K^+ stimulated dopamine release in rat nucleus accumbens (Thompson and Moss, 1994), all without affecting gene transcription.

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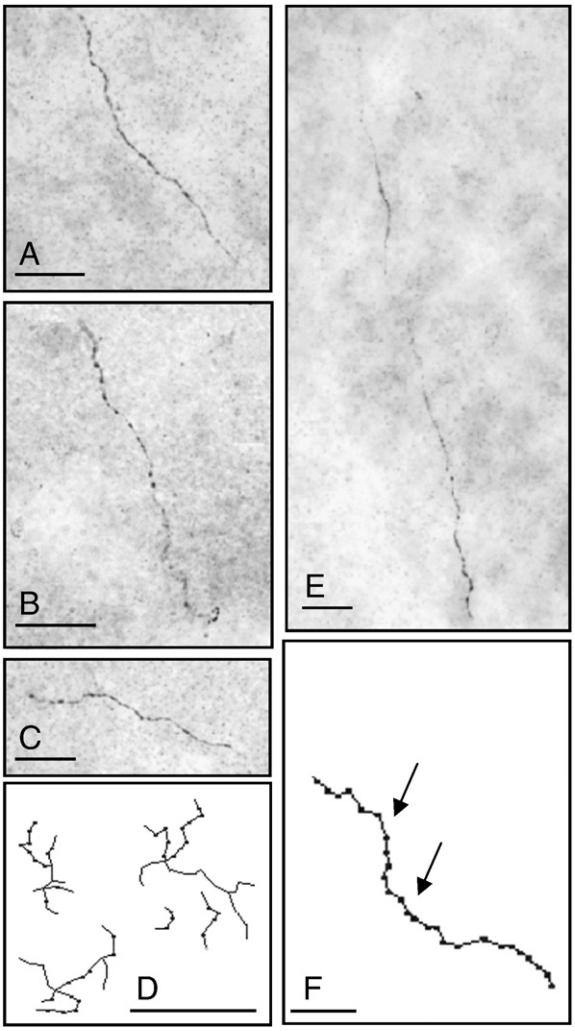

Fig. 1. Morphology of AR-ir axons in the adult male rat brain. A–C, E: Digital images of AR-ir axons in the A. piriform cortex, B. amygdala, C. hippocampus E. entorhinal cortex, D. Tracing of AR-ir terminal field in the entorhinal cortex; E. Tracing of AR-ir axons in the piriform cortex with arrows indicating punctate stain. Scale bars represent 25 μm.

Over the last 30 years, biochemical, molecular, and additional physiological studies have added to our understanding of the rapid, non-genomic actions of estrogen, progesterone, glucocorticoids, mineralcorticoids, thyroid hormone, vitamin D, and androgens (for review, see Schmidt et al., 2000). This evidence has broadened the view of what the steroid receptor family of proteins is capable of, although the mechanisms remain to be fully characterized. Newer behavioral evidence from several labs (for example, see Bass and Remage-Healey, this issue) has provided a systems-level analysis of what the rapid actions of steroids mean in the context of the nervous system and whole organism. In contrast, relatively few studies have been able to establish a neuroanatomical basis for these rapid actions. With the immunohistochemical observations on extranuclear localization of androgen receptor (AR) reviewed below and other information about the rapid actions of androgens in cells and whole organisms, we may begin to obtain a clear understanding of the role of extranuclear AR in the nervous system.

Evidence of androgen receptors in axons and other non-nuclear locations

Recently, we identified AR-immunoreactivity in axons and dendrites in the adult male rat cerebral cortex and amygdala (DonCarlos et al., 2003, 2006) (Figs. 1 and 2). No AR-immunoreactive (AR-ir) neurites were present in the hypothalamus, preoptic area or bed nucleus of the stria terminalis, brain regions with abundant nuclear AR. At the light microscopic level, we identified these neurites as axons. The axons were small in diameter and punctate in appearance. At the ultrastructural level,

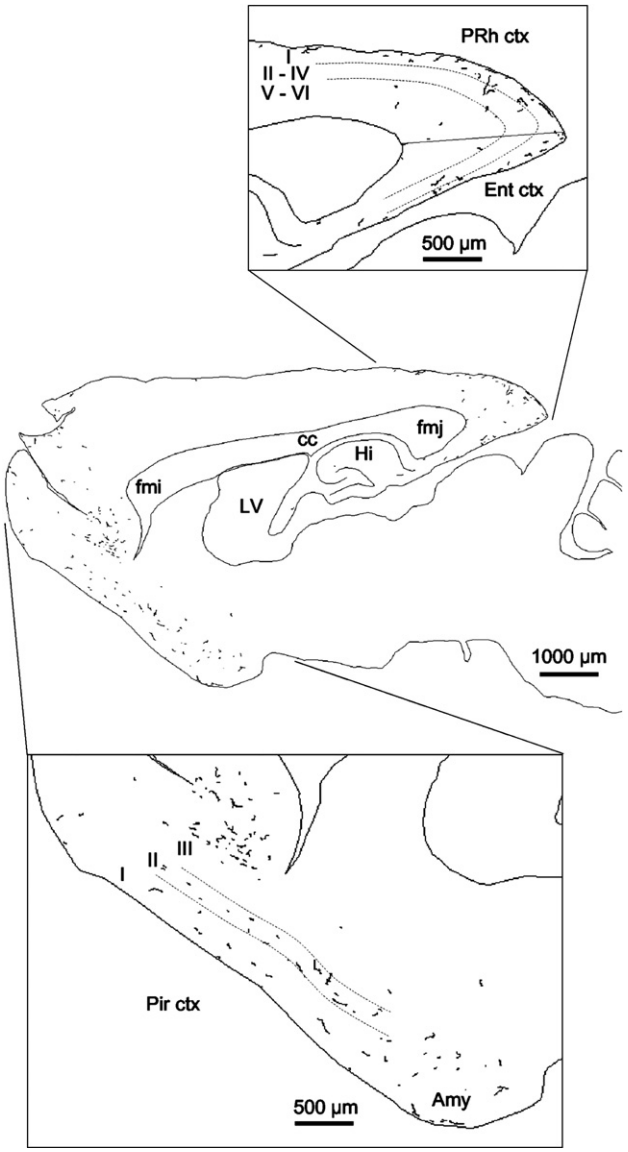

Fig. 2. Distribution of AR-ir axons in the rat forebrain and brainstem. This map was produced using NeuroLucida software (MicroBrightField Inc.) and illustrates a single 40-μm parasagittal section, 2.9 mm lateral to bregma. The entire section was scanned at 40X, and all AR-immunoreactive axons observed were traced. An adjacent Nissl-stained section was used to delineate cortical layers. Amy, Amygdala; cc, corpus callosum; ctx, cortex; Ent, entorhinal cortex; fmi, forceps minor of the corpus callosum; fmj, forceps major of the corpus callosum. Hi, hippocampus; LV, lateral ventricle; Pir, piriform cortex; PRh, perirhinal cortex. Reproduced from (DonCarlos et al., 2003), Copyright 2003, The Endocrine Society.