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ANDROGEN MODULATION OF HIPPOCAMPAL SYNAPTIC PLASTICITY

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Abstract—This review briefly summarizes recent developments in our understanding of the role of androgens in maintaining normal hippocampal structure. Studies in rats and vervet monkeys have demonstrated that removal of the testes reduces the density of synaptic contacts on dendritic spines of cornu ammonis 1 (CA1) pyramidal neurons. This effect is rapidly reversed by treatment with either testosterone or the non-aromatizable androgen dihydrotestosterone, suggesting that maintenance of normal synaptic density is androgen-dependent, via a mechanism that does not require intermediate estrogen biosynthesis. Similar effects of these androgens are observed in ovariectomized female rats, except that in the female the actions of testosterone include a substantial contribution from estrogen formation. The ability to stimulate hippocampal spine synapse density is not directly related to systemic androgenic potency: thus, weak androgens such as dehydroepiandrosterone exert effects that are comparable to those of dihydrotestosterone; while partial agonist responses are observed after injection of the synthetic antiandrogen, flutamide. These data provide a morphological counterpart to observations that androgens enhance cognitive function and mood state, suggesting that these effects may result at least in part from hippocampal neurotrophic responses. The unusual specificity of these responses raises the possibility that effects of androgens on the brain may be mediated via different mechanisms than the masculinizing actions of these steroids in non-neural androgen target organs. © 2006 Published by Elsevier Ltd on behalf of IBRO.

Key words: dihydrotestosterone, dehydroepiandrosterone, flutamide, spine synapse density, CA1 hippocampal area.

A few years ago, Breedlove and Jordan (2001) published an editorial which pointed out how tenuous some of the classical concepts of neuroanatomy had become, in light of new research findings showing that the mature CNS retained a good deal of structural plasticity. The immediate purpose of this editorial was to highlight the elegant work of Yankova et al. (2001) on estrogen-induced synaptic remodeling in the hippocampus; but in so doing it also brought into sharp focus how much the conventional view of the adult brain as an anatomically "fixed" structure had changed. In the intervening period, the pace of new developments has accelerated, resulting in widespread acceptance of the idea that even the adult mammalian brain retains considerable structural plasticity. Neurogenesis continues in adulthood, while synapses are dynamically lost and reformed, sometimes with extraordinary rapidity. We are beginning to understand that this plasticity probably plays a vital role not only in normal behavior, but also in pathophysiological events leading to the development of neurological disease states. All of this has evolved from a most unexpected source: the initial observations and much of the ensuing evidence supporting a role for dynamic plasticity in the adult brain have come from observations on the effects of steroid hormones, the gonadal steroids playing a particularly important role.

Much of the work on gonadal steroid–induced neuroplasticity has focused on the effects of estrogen, which participates in orchestrating sexual differentiation in development as well as modulating adult hypothalamic and hippocampal structure. A separate paper in these proceedings reviews the work in this field (Parducz et al., 2005). The purpose of the present article is to summarize recent work on the second major family of gonadal steroid hormones, the androgens, which now also appear to exert important effects on hippocampal synaptic plasticity.

Evidence for neurotrophic effects of androgens

The growth, differentiation, normal physiology and aging of the CNS are all now recognized to be influenced by gonadal steroid hormones. Steroids arriving from the gonads via the circulation modulate the responses of the brain, affecting not only sex behavior and sexually differentiated stereotypical behavioral responses, but also the ability of the brain to process, store and retrieve sensory information (Luine, 1997; Dohanich, 2002).

Changes in gonadal steroid levels over the course of the normal lifespan contribute not only to variations in cognitive function, but also to the incidence of certain types of neurodegenerative disorder. Perhaps the most dramatic example of this has come from work examining the factors contributing to Alzheimer's disease (AD). Although the issue remains controversial, a number of studies have reported that the incidence of AD may be reduced in postmenopausal women who have taken estrogen-based

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Abbreviations: AD, Alzheimer's disease; androstenediol, androst-5-ene-3β,17β-diol; CA1, cornu ammonis 1; DHEA, dehydroepiandrosterone; DHT, 5α-dihydrotestosterone; FF, fimbria-fornix; HRT, hormone replacement therapy; 3αA-diol, 5α-androstan-3α,17β-diol.

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hormone replacement therapy (HRT), particularly when HRT was initiated soon after menopause (Paganini-Hill and Henderson, 1996; Tang et al., 1996; Yaffe et al., 2000; for review see Sherwin, 2003).

While relatively less attention has been devoted to the effects of androgens, these steroids also clearly have positive effects on cognitive performance, in human beings as well as in laboratory animals (Flood et al., 1995; Dohanich, 2002; Bimonte-Nelson et al., 2003; Hirshman et al., 2004; Salminen et al., 2004; Janowsky et al., 2000). In addition, androgens appear to have well-characterized positive effects on mood state (Barrett-Connor et al., 1999; Delhez et al., 2003). In both men and women, androgens comprise a substantial component of the total circulating pool of gonadal steroids in young adults, but then decline markedly with age. Circulating levels of the adrenal androgen dehydroepiandrosterone (DHEA), in particular, undergo a precipitous decline over the course of middle age, declining more than 70% between the 3rd and 6th decades of life (Labrie et al., 2003; Almeida et al., 2004). Recent work provides tantalizing hints that maintenance of androgen levels may be at least as important as that of estrogens, in terms of minimizing the risks of neurodegenerative disorders. Studies on adrenal steroid levels in AD patients have demonstrated a reduction in the circulating concentrations of testosterone and DHEA-sulfate, in comparison to normal controls (Sunderland et al., 1989; Yanase et al., 1996; Hogervorst et al., 2001). A recent National Institute of Aging study reported that older men with low levels of free circulating testosterone appear to be at higher risk of developing AD than men with higher serum levels of this hormone (Moffat et al., 2004).

Androgen action in the brain: the role of local metabolism

One of the complexities in understanding the effects of androgens is that these steroids have a very broad spectrum of activity. At least in part, this is because androgens represent substrates for the synthesis of several biologically active metabolites. The production of these metabolites amplifies and expands the intracellular actions of the circulating hormones (for reviews, see Bardin and Catterall, 1981; Labrie et al., 2003). Testosterone is converted to estradiol and several 5α-reduced androgens, in neurons as well as glia (Martini et al., 1993; Zwain et al., 1997; Zwain and Yen, 1999). The immediate product of testosterone reduction, 5α-dihydrotestosterone (DHT), is more potent than testosterone in bioassays of androgenic activity. Further metabolism of DHT results in the formation of 5α-androstan-3α,17β-diol (3αA-diol) as well as its 3β-isomer (3βA-diol), both of which are capable of eliciting estrogen receptor-dependent responses (Ginsburg et al., 1977; Pak et al., 2004). 3αA-Diol also acts like the analogous metabolites of progesterone and corticosterone, to enhance GABA-benzodiazepine regulated chloride channel function (Frye et al., 1996a,b). Other weak circulating androgens, such as DHEA, may exert their effects, at least in part, by acting as substrates for intracrine conversion to testosterone and DHT in androgen target tissues (Labrie et al., 2003). They can also potentially act via the formation of metabolites analogous to those produced from testosterone: DHEA is extensively converted to androst-5-ene-3β,17β-diol (androstenediol) by 17β hydroxysteroid dehydrogenase. Androstenediol, like 3βA-diol, has significant estrogenic bioactivity (Ho and Levin, 1986; Littlefield et al., 1990). DHEA and its principal circulating metabolite, DHEA-sulfate, have been demonstrated to exert a wide range of direct effects on neuronal function (Ueda et al., 2001; Kaasik et al., 2003; Sullivan and Moenter, 2003).

Effects of androgens on CNS morphology

The demonstration by Woolley et al. (1990), Gould et al. (1990), and McEwen et al. (1995) that the ovarian steroids dynamically regulate the density of synaptic contacts on the dendritic spines of cornu ammonis 1 (CA1) pyramidal cells during the female reproductive cycle fundamentally changed our understanding of how gonadal steroids interact with the hippocampus. There is extensive evidence that regulation of dendritic connectivity in the hippocampus may play a critical role in the formation of memory (Geinisman et al., 2001; Kasai et al., 2003; Lang et al., 2004). These observations led naturally to the hypothesis that modulation of hippocampal synaptogenesis might contribute to the effects of gonadal steroids, including androgens, on cognitive behavior.

An extensive body of evidence already indicated that androgens exert “organizational” effects on the structure and function of the hippocampus, during development. In some strains of mice, males have more granule cell neurons in the hippocampal dentate gyrus than females (Wimer and Wimer, 1989). Likewise, male rats have a larger and more asymmetric dentate gyrus than females (Roof and Havens, 1992; Roof, 1993), while sex differences have been demonstrated in the apical dendritic structure and the dendritic branching patterns of CA3 pyramidal neurons. Since the apical dendrites of CA3 pyramidal cells are the targets of afferent mossy fiber synapses from the granule cell layer of the dentate gyrus, these observations are consistent with the hypothesis that there is increased input from the dentate gyrus, in males as compared with females (Parducz and Garcia-Segura, 1993).

In adulthood, several studies over the last five years have provided indications that the hippocampus may retain some degree of androgen-regulated neuroplasticity. Shors et al. (2001) reported sex differences in hippocampal spine density and responses to stress of CA1 dendritic spines, suggesting that testosterone might play a role in modulating hippocampal dendritic anatomy. A number of studies demonstrated effects of androgens on hippocampal electrophysiological and morphological responses in the rat (Harley et al., 2000; Smith et al., 2002; Hebbard et al., 2003).

We initially hypothesized that these effects might at least in part reflect effects of androgens on the formation of hippocampal dendritic spine synapses, paralleling previous work on the effects of estrogens (Woolley and McEwen, 1992). To test this hypothesis, we determined whether removal of the testes might alter hippocampal spine synapse density. Studies in both rats (Leranth et al., 2003) and a representative sub-human primate, the St. Kitts vervet monkey