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Introduction: The end of sex as we once knew it

Bruce S. McEwen *

Laboratory of Neuroendocrinology, The Rockefeller University, Box 165, 1230 York Avenue, New York, NY 10065, United States

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ABSTRACT

This special issue of *Physiology and Behavior* is devoted to papers summarizing sex differences that are now recognized to include not only reproductive behaviors, but also non-reproductive processes and phenomena such as feeding, thirst, pain, sensory processes, mood, cognitive function, the effects of stress, and the propensity for drug abuse. The purpose of this brief introduction is to trace some of the main themes and historical highlights in the discovery that the entire nervous system appears to be a target of reproductive hormones, as well as being subject to developmentally programmed sex differences.

The study of sex hormone action and sex differences in the brain began with investigating the effects of testicular secretions on reproductive behavior and function [1,2]. Yet, until the 1960's, there was doubt that sex hormones even entered the brain [3]. However, the use of discrete hormone implants into the hypothalamus demonstrated that estrogens and androgens activate reproductive behaviors [4,5]. Concurrently, the use of tritiated steroid hormones and the technique of steroid autoradiography revealed the presence of binding sites for these steroids that resemble the cell nuclear receptors that were demonstrated by tritiated steroid binding in uterus and other reproductive organs (see [6]).

Sex differences in reproductive function were first uncovered by manipulations of gonadal hormones in rodents immediately after birth [7,8]. Subsequent studies revealed morphological sex differences in hypothalamus [9,10] and also in spinal cord [11]. Subsequent work extended these findings to the human hypothalamus [12–14]. All of this important knowledge has now been supplemented and enriched by findings outside of the hypothalamus. Indeed, the notion that the hypothalamus and sexually dimorphic nucleus of the spinal cord are not the only areas of the CNS where sex hormones act and where sex differences exist was initially suggested by findings in Parkinson's Disease, the neuroanatomy of the corpus callosum and estrous cyclicity of seizure sensitivity in the hippocampus.

The Parkinson's connection arose with the observation that high dose estrogen treatment used in the initial contraceptive preparations exacerbated symptoms of Parkinson's Disease in women [15]. This was very unexpected for those who believed in the nuclear estrogen receptor story because there are no cell nuclear estrogen receptors in the rodent striatum, and yet tiny unilateral implants of estradiol in the rodent striatum elicited unilateral rotation associated with imbalanced dopaminergic function [16]. Furthermore, estradiol regulates dopamine release from striatum in a sexually-dimorphic manner [17].

The corpus callosum and anterior commissure emerged as brain regions that differ in shape between men and women [18,19] and which, therefore, may be influenced by hormone in early development. More recent studies also showed morphological sex differences in the cellular organization of the human temporal lobe [20,21].

Studies on the hippocampus revealed large differences across the rodent estrous cycle in the seizure threshold — with proestrus females showing greater sensitivity (lower thresholds) than diestrus females [22]. This was followed by the finding of estrogen-induced spine synapse induction in hippocampus [23,24], which also was surprising because, like the striatum, there were very few nuclear estrogen receptors in the hippocampus [25,26]. The hippocampus has also turned out to be a target of sexual differentiation, with sex differences in spatial memory acquisition [27] and in sex hormone activation of synaptogenesis [28] that are reversed by the presence or absence of testosterone in neonates [29]. But the hippocampus has very few cell nuclear estrogen receptors except in inhibitory interneurons [30] and this finding led to further studies of estrogen's mechanism of action.

Indeed, a critical advance in the puzzle of gonadal hormone actions where there are no detectable cell nuclear receptors was the finding, using electron microscopic immunocytochemistry that estrogen receptors occur outside the nucleus in dendrites, presynaptic terminals and astroglial processes [31]. These receptors, which have recently been shown to bind radioactive estradiol [32], appear to signal rapid non-genomic actions via phosphorylation of second messenger systems such as PI3 kinase and Akt, LIM kinase1, MAP kinases, trk B neurotrophin receptors and CREB [31,33–39].

* Tel.: +1 212 327 8624; fax: +1 212 327 8634.
E-mail address: mcewen@rockefeller.edu.

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Non-genomic estrogen receptors were also detected in brain regions, such as corpus striatum and cerebellum [31,40]. Moreover, a growing body of evidence indicates the presence of receptors for testosterone, progesterone and glucocorticoids in non-genomic sites [41–43]. Thus, non-genomic signalling pathways are likely to be involved in the actions of these steroid hormones on the nervous system.

A related aspect of steroid hormone actions on structural plasticity in the brain is their dependence on concurrent excitatory amino acid neurotransmission, as revealed by studies showing effects of estrogens on synapse formation [44] and of glucocorticoids on dendritic remodeling [45,46]. Excitatory amino acid neurotransmission is vital to the ability of the brain to encode memories of experiences, and experience is also capable of changing the brain both structurally and functionally [47]. Because of their actions on the brain, as described above, hormones, through their synergistic actions with neurotransmitters, are able to bias the nervous system towards adopting certain strategies for learning or other behavioral responses (e.g., see [48]). Likewise, the process of sexual differentiation interacts with experience to produce sexually dimorphic patterns of behavior [for a masterful discussion of this topic, see [49].

Thus, recent advances in the study of sex hormone action and sex differences are challenging the long-held dogma that only the reproductive aspects of brain function are affected by sexual differentiation and by sex hormones. Rather, we now are beginning to understand that the entire brain is, to varying degrees, a target of gonadal hormones and a potential site of developmentally-programmed sex differences. This is made even more interesting and complex by the realization that there are also sex differences that are chromosomally linked [50–52]. The future prospects for this line of research are both challenging and highly relevant to many aspects of neuroscience, behavioral biology and medicine [53,54].

[1]Quote from End of sex as we know it: by B.S. McEwen and E.N. Lasley (2005)

> "Right now, the research is raising as many questions as it is answering, at least when it comes to definite conclusions about human behavior and many brain functions. It goes without saying, or should, that the existence of important sex-based brain differences does not mean in any way, shape, or form, that a stronger or more intelligent sex exists. Several animal studies, however, are clarifying the specific differences in males and females and how chemistry, genetics, and the environment play their parts in creating divergent results depending on sex. Scientists suspect that the observable differences in performance of men and women in various areas are produced by some combination of genetic and environmental influences that bring about the distinct, sometimes dramatic, divergence in pathways of brain and behavior that is emerging from new research."

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