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DOGMAS AND UNSOLVED PROBLEMS IN BRAIN SEX DIFFERENTIATION

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Throughout the animal kingdom, nervous systems differ between sexes. Sexual dimorphisms in neuroanatomical, physiological, and neurochemical parameters are reflected by sex-specific forms of behavior, in particular with regard to reproduction, and sex differences in neuroendocrine regulation. The present volume of *Biomedical Reviews* is mainly concerned with sex differences in the mammalian and human brain. However, it should at least be mentioned that the most convincing correlations between neuroanatomical and behavioral data have been provided by studies of the sexual differentiation of song control systems in bird species, in which the males sing and the females do not. In mammals, research used to locus on the hypothalamus commonly seen as the center for control of reproductive behavior and integration of hormonal and neural responses of the organism. We have therefore asked A Mafsumofo and %. /*ra/ to review the evidence for the hypothesis that sexually dimorphic functions of the hypothalamus are indeed based on a sex-specific neural circuitry. Notwithstanding the central role of the hypothalamus, it is important to note that more and more, often subtle, anatomical and/or functional sex differences have been and continue to be detected in other areas of the central nervous system. Of particular interest are sex differences in neural systems than are known to modulate the functional circuitry throught the brain, such as subpopulations ofy-aminobutyric acid-ergic (Sfe/anot/a 6f a/, this volume) and catecholaminergic neurons (1). Finally, it would be surprising if correlations of sex-specific behaviors were not detectable in the organization of brain structures involved in the control of such behavior, i.e. the limbic system and the cerebral cortex. That this is indeed the case, will become evident from the contributions of O.F. Si/i/aa6 ef a/and D. K7mura, whose focus is on the human brain and human behavior.

Current dogma holds that sexual dimorphisms in the vertebrate brain are generated by the epigenetic action of gonadal hormones. The mechanisms would be analogous to those involved in development of the mammalian reproductive tract from a bipotential anlage. The classical "organizational" hypothesis, derived from behavioral research on mammals, is that androgens organize male-type brain circuitry irrespective of the genetic sex. Androgen, after entering the brain, may be aromatized to estradiol-17B, the steroid thought to be responsible for the establishment of a male brain. Conceptually, these "organizing" effects, occurring during a critical period or time-limited window in development, are distinguished from the "activating" effects of gonadal hormones on the adult brain (2).

The conventional view of gonadal steroids being the sole determinants of sex differences in the brain has met with criticism. One of the sources of doubt is the disparity of observations in the literature on how gonadal steroids affect developing neurons. This alone suggests that no simple relationship exists between sex differences in levels of circulating gonadal

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steroids and the acquisition of sex-specific properties by the vertebrate brain (3). Another argument comes from clinical observations. Several mutations have been detected in humans thai disrupt the function of sex steroid receptors or the cytochrome P450 enzyme aromatase, but do not result in disorders of brain development which would have been expected on the basis of the steroid hypothesis (4-6). It is therefore justified to assume that sexual differentiation of the mammalian brain is not only controlled by an extrinsic signal from the gonads but also by a number of additional factors or mechanisms that may reside within the brain. As *C. Beyer and J.B. Hutchison* describe in their contribution, regulation of the production of esIrogcns from androgen within brain cells by P450 aromatase is likely to generate a sex-specific hormonal microenvironment, which may be quite independent from thai provided by the genera] circulation. Another important aspect of the regulation ol'slcroicl hormone action in the developing brain is brought up by *R.J. Handa et ah* How is the cellular expression of androgen or estrogen receptors controlled during ontogenesis? Besides steroid hormones, other forms of intercellular communication may participate in shaping a sex-specific microenvironmenl for a developing neuron. As an example, *M.C. Fernandoz-Galaz et al* consider interactions taking place, during brain development, between gonadal steroid hormones and neurotrophins/growlh factors. Not only do estrogens modulate synthesis of growth factors and expression of growth factor receptors in neurons or glia but also the reverse is shown to happen. Signal transduction from growth factors may even activate estrogen receptors, in the absence of Ihe steroid ligand, by protein kinase-depcndent phosphorylation. Here one might add that this kind of cross-talk between plasma membrane and cytosolic receptors is also possible with respect to neurotransmitter signaling (7). Furthermore, estrogen receptor action may also be interfered with on the genomic level. Frequent targets of membrane receptor-activated pathways in nerve cells are activator protein-1 transcription complexes and these can interact with or compete with estrogen receptors for binding sites on promoters of neural genes (8). By any of these mechanisms, neuron-to-neuron or glia-to-neuron signaling could regulate the steroid sensitivity of a neuron and create individual time windows for effects of sex steroids.

Finally, apart from environmental cues for developing neurons, there appears to be the potential for cell-autonomous decisions of sexual fate of single cells. Based on observations made in cell cultures from embryonic rodent brain (9-14), we have previously proposed that mammalian nerve cells are capable of reali/.ing their genetic sex independently of a sex-specific hormonal environment (15). This kind of developmental control would be basically similar to the one involved in primary sex determination of the organism where a regulatory cascade of sex chromosomal and autosomal genes is believed to initiate differentialion of a lestis from an indifferent gonad. It is therefore appropriate lo include a contribution of *U. Mittwoch,* who reviews currenl knowledge aboul Ihe genes involved in Ihe conlrol of sexual differentiation of Ihe gonad and, thus, sex determination of the mammalian organism. Another line of evidence for direct | genetic influence on development and maintenance of sex-specific traits of mammalian nervous systems comes from genetic and behavioral studies on specific mouse strains. S. *Maxson* discusses various possibilities how sex chromosomal and autosomal genes could differentially influence brain and behavior of males and females.

Hopefully the reader of this special volume of *Biomedical Reviews* will realize that the regulation of Ihe sexual differentiation of the mammalian brain is most probably a lot more complex than hitherto believed. As is the rule in many developmental processes, cell differentiation appears to be controlled by an interplay between cell-aulonomous decisions and environmental cues. With regard to sexual differentiation, this principle is beautifully illustrated in Ihe nematode *Caenorhabditis elegans,* where sex-specific intercellular signaling serves to coordinate cell-autonomous decisions made by individual somatic cells (16). In analogy, in the mammalian brain, there would also be the potential for neurons to realize and maintain their genetic sex cell-autonomously. Intercellular signaling by means of steroid hormones, growth factors, and synaptic communication would then be necessary to orchestrate such cellular events with respect to the sexual fate of the entire brain.

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