Preface

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The Tenth Annual Karger Workshop was held in conjunction with the regular meeting of the J.B. Johnston Club in Los Angeles, Calif. (November 7, 1998). The theme of the workshop, 'Steroid Action on Brain and Behavior' was intended to provide a general and comparative overview of steroid action on brain and behavior from an evolutionary perspective. To this end, the order of talks was gauged towards a better understanding of the underlying mechanisms that mediate steroid action on brain and behavior. The first three talks considered how steroids organize, activate, and modify the structure and function of neural systems in mammals (Marc Breedlove), birds (Greg Ball; Juli Wade) and reptiles (Juli Wade). The next two talks focused on the cellular and molecular mechanisms that mediate brain-steroid interactions in vertebrates (Frank Moore and Harold Zakon). The last talk (Janis Weeks) consolidated many of the above ideas by addressing how steroids interact at molecular and cellular levels to reorganize neural circuits and behavior during insect metamorphosis. In the spirit of the J.B. Johnston Club, the workshop generated lively discussions on new and established theories on steroid action on brain and behavior from comparative and evolutionary perspectives. The articles contained within this issue expand on these issues by providing new ideas and fresh insights into how steroids act in the brain to bring about changes in behavior.

In the first paper, Marc Breedlove (special invited guest), summarizes the 'orthodox' view of mammalian sex differentiation as it pertains to the organizational hypothesis, which contends that the same steroid that induces the periphery to form a masculine phenotype also permanently organizes the developing brain in a masculine manner. He

then illustrates why this classical view may be over simplified by considering how androgens influence the sexual differentiation of motoneurons in the spinal nucleus of the bulbocavernosus (SNB). He admits that many aspects of the SNB system can be explained by the classical organizational hypothesis. Androgens in males act early in development to masculinize the system by sparing the loss of SNB motoneurons and their target muscles. In the absence of perinatal androgens, the system is organized in a female fashion with fewer motoneurons and less muscle fibers. Nevertheless, other aspects of the system do not appear to fit the classical model. For example, recent evidence suggests that the masculinizing effects of androgens may be partly dependent on other mediating factors, such as environmental cues and/or social interactions. There is also evidence that androgens can influence the organization of the system in adulthood. Thus, the SNB system displays a far richer array of interactions than the orthodox view of sexual differentiation would predict.

Breedlove's arguments are provocative because they warn against the tendency of fitting results to preexisting models without taking other explanations into account. He also implies the need to ask more questions about the diversity of mechanisms that underlie sexual differentiation from a comparative perspective. He suggests that this will not only provide insight into the evolution of those mechanisms, and the commonalties they share, but also the unique ways in which particular species have solved particular problems.

In the second paper, Juli Wade first outlines general principles that underlie sexual differentiation of brain and behavior in mammals. One principle is that the tests of developing males secrete testosterone that is converted to

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estradiol in the brain by aromatase; estradiol then induces permanent neurological changes that result in the display of male sexual behavior in adulthood. She then presents evidence that the mechanisms that regulate sexually dimorphic courtship systems in zebra finches and green anole lizards do not necessarily play by mammalian rules. Of particular interest is her recent work on zebra finches. It is generally accepted that the central conversion of testosterone to estradiol is responsible for masculinizing vocal control nuclei and singing behavior. However, Wade presents intriguing evidence that argues against this concept. For example, if estrogenic metabolites play an important role in the process, then aromatase inhibitors, such as Fadrozole, should decrease the masculinization of male vocal control centers and singing behavior. Surprisingly, this does not appear to be the case. Fadrozole administered to embryonic and post-hatching males does not prevent the masculine development of song control nuclei, nor does it reduce singing behavior in adulthood. Thus, contrary to the accepted mammalian model, Wade's findings suggest that gonadal steroids may not be solely responsible for masculinizing the morphology and function of the song system. She is now exploring whether steroids interact with neurotrophins and/or insulin-like growth factors to promote the normal development of the song control system in males.

It is also commonly accepted that steroid receptors are evolutionarily conserved in the brains of vertebrates. However, the recent identification of two forms of estrogen receptors in mammals has raised new questions about the functions of steroid receptors in the brain. Thus, comparative studies on the central localization of estrogen receptor α (ER α) and estrogen receptor β (ER β) in non-mammalian vertebrates would be expected to provide valuable information to confirm and/or extend existing theories on the function of these receptors. One hypothesis that has emerged from mammalian studies is that ER α plays an important role in regulating reproductive functions, while ER β is more important for non-reproductive events such as learning and memory.

In the third paper of this issue, Ball and co-workers address the general applicability of the above hypothesis by comparing the distributions of ER α and ER β in the brains of Japanese quail and European starlings. In quail, the localization of ER α was found to be similar in many respects to the general pattern observed in rodents. However, the extra-hypothalamic distribution of ER α was not as extensive as that described in mammals. Interestingly, ER β was found to be localized in regions that regulate reproductive functions as observed in mammal species as well. However, the function of ER β in these regions is still open to speculation since

ER α 'knock-out' mice do not engage in reproductive behaviors. Their work on European starlings focused primarily on the vocal control regions that are unique to oscine songbirds. ER α was found to be present in the nucleus HVC (Higher Vocal Control Center), but not in other song nuclei. ER β was not identified in any song control region, but was present in other areas of the brain including sites that mediate sexual behavior. Since HVC has evolved to coordinate the production of courtship songs with other aspects of reproduction, the presence of ER α in this region is consistent with the hypothesis that this receptor sub-type is involved in the regulation of reproductive behavior. However, as Ball and his co-authors point out, the widespread distribution of ER β in other reproductive centers suggests that one must be cautious about the generality of current hypotheses until more is known about the function of ER β in these regions. Thus, their work in this area will not only help to elucidate steroid function in avian species, but also contribute to the development of conceptual generalizations on the functional significance of vertebrate steroid receptors.

The fourth paper by Moore and Evans directly complements the preceding paper because it addresses alternate mechanisms of steroid action on brain and behavior. Until recently, all steroid hormones were believed to bind to intracellular receptors which functioned as ligand-dependent gene transcription factors. Although this classic genomic model for steroid action can explain the molecular mechanisms for some steroid responses, it is becoming increasingly obvious that other types of responses involve non-classical, non-genomic, mechanisms. In support, Moore and Evans reviews evidence that steroids can: (1) bind to receptors in the plasma membrane, (2) activate a variety of second messenger systems, and (3) regulate a wider range of functions on a broader time scale, from microseconds to days. They conclude that steroid hormones use several types of receptors and multiple cell signaling pathways and do not function only as modulators of gene transcription. As Moore and Evans stress, one should not assume that minute-to-minute changes in steroid concentrations do not trigger biologically important, short-term events, nor that the only steroid hormones with biological functions are those that bind with high affinity to intracellular steroid receptors.

Janis Weeks' paper consolidates many of the above ideas by considering how ecdysteroids function to reorganize the central nervous system and alter behavior during metamorphosis in the hawkmoth, *Manduca sexta*. More specifically, the paper describes how a class of motoneurons undergo dendritic regression and regrowth, and segment-specific programmed cell death, in response to specific ecdysteroid

cues. Not surprisingly, there are many interesting parallels between this system and the vertebrate models described above. For example, steroids play an important role in regulating programmed cell death in *Manduca*, the mammalian SNB, and songbird vocal control centers. Likewise, steroid-induced changes in dendritic morphology occur in both vertebrates and invertebrates. Because there are other examples as well, the reader comes away with two important messages. The first is that the evolutionary conservation of steroid receptors, and the parallels between steroid action on insect and vertebrate neurons, suggest that underlying mechanisms may be shared. The second is that comparative studies on both vertebrate and invertebrate species can yield important information for elucidating steroid action on brain and behavior.

The final paper by Zakon and Dunlap is clearly written from an evolutionary perspective. They focus on two closely related species of weakly electric fish (brown ghosts, *Apteronotus leptorhynchus*; and black ghosts, *Apteronotus albifrons*) which exhibit different sexual dimorphisms in their electric organ discharge (EOD) frequencies, and their propensity to produce social communication signals known as chirps. Male brown ghosts emit at higher EOD frequencies than females, while the situation is reversed in black

ghosts. Interestingly, non-aromatizable androgens raise EOD frequency in brown ghosts, but have the opposite effect in black ghosts. In addition, androgens induce chirping in female brown ghosts, but do not influence chirp propensity in female black ghosts. They suggest that the variation in sexually-dimorphic communication signals between the two species is mediated by differences in their responses to sex steroids. More importantly, their paper provides valuable insight into how neural circuits have evolved in distant and closely related species to respond differently to the same steroidal signals.

In closing, I would like to thank all of the contributors for their enthusiasm and willingness to participate in the workshop, and for their timely submissions of their manuscripts. We thank Dr. Thomas Karger for his continued support of the workshop series and the annual meetings of the J.B. Johnston Club. We are indebted to the individuals who helped with the lights and slide projection during the workshop, and the audience for providing open and lively discussions. Finally, I would like to express my gratitude to Laura Bruce for the time and effort that she put in to organizing the annual meeting. Without her involvement, the meeting would not have been a success.