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Neurobiological Correlates of Masculine Sexual Behavior

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MAS, M. *Neurobiological correlates of masculine sexual behavior.* NEUROSCI BIOBEHAV REV 19(2) 261-277, 1995.— The experimental analysis of the neuroendocrine interactions regulating sexual behavior has traditionally relied on studying the effects of CNS lesions and pharmacological treatments with hormones or drugs purportedly acting through specific neurotransmitter systems. New methodological developments have allowed the assessment of several indices of neural function in experimental animals, particularly the rat, as they relate to behavioral changes. In the field of sexual behavior, ex vivo analyses have been used to measure markers of energy metabolism, such as 2-deoxyglucose uptake and Na,K-ATPase activity, the tissue content of neurotransmitters and metabolites, the levels of steroid receptors and neurosteroids, and immediate-early gene expression products in different areas of the CNS. In vivo studies have monitored brain electrical activity and temperature, as well as the extracellular levels of neurotransmitters and metabolites by cerebrospinal fluid sampling, push-pull perfusion and, especially, electrochemical recordings and microdialysis, in the course of mating and exposure to various relevant stimuli. The findings with the different methodologies are generally consistent and agree with those of previous surgical and pharmacological manipulations. They provide data on temporal relationships between neurobiological and behavioral events and suggest new interpretations for different aspects of the male copulatory pattern.

Male sexual behavior Na,K-ATPase Estrogen receptors c-*Fos* expression Electrical activity
Temperature In vivo voltammetry Microdialysis Dopamine Serotonin Neuropeptides Prolactin

IN contributing with this article to honor Julian Davidson I am not only paying tribute to the outstanding scientist and dear friend. It is also the payment of a debt. My interest in the study of neurochemical concomitants of sexual behavior grew up, in great part, in the course of many stimulating discussions with Julian during my stay in his laboratory as a visiting scientist. We became aware of the difficulties of drawing conclusions about the physiological role of brain neurotransmitters from drug effects only, as was commonly done in the field of basic sexual research. When returning to my home laboratory in 1985, the decision had been already made to looking in the future at sexual behavior from this, at the time, rather unusual angle. We kept exchanging fruitful visits for years afterwards, with Julian being eventually awarded a Honoris Causa Doctorate by the University of La Laguna. As a result of this continued interaction we co-authored what was my first report on this topic, and a very early one in the field (120). The present title is reminiscent of that joint paper.

Elucidating the neurobiological mechanisms of goal-oriented behaviors represents, indeed, a most challenging task as they result from multiple interactions between environmental, hormonal and neural signals, mediated by a wide variety of chemical messengers, which are integrated at different levels of the CNS. The assessment of mating behavior of laboratory animals, particularly the rat, has provided long since a fruitful model for studying such processes. The highly stereotyped pattern of sexual behavior shown by this species allows the use of remarkably consistent behavioral measures analyzing its different components (see 37 for a description of methods). Detailed behavioral analyses of sexual activity of the male rat have led to elaborate conceptualizations about the interplay of its motivational and consummatory components (e.g., 15,58,163). The induction of sexual behavior by gonadal steroids in both male and female rats, a field in which Julian's laboratory has excelled for decades, provides the clearest demonstration of the ability of hormones to influence behavioral processes. Likewise, the CNS areas which are required for the expression of the different components of the male mating pattern have been throughly investigated in this species by lesion and stimulation experiments.

Moreover, the changes in male rat sexual behavior induced by neurotropic drugs has been widely investigated (for reviews see 20,163). Since many of these substances are thought to act through relatively well-defined neurotransmitter systems, their effects have helped to generate hypotheses about the neurochemical mechanisms regulating reproductive behavior, although the direct evidence has been lacking until recently. This approach has proved useful in many respects. An important one is that of its practical implications, since it can help in the development of therapeutic agents for human sexual

disorders. Yet, its use as a tool for analyzing the underlying neural phenomena is more problematic inasmuch as it is based on the assumption that the drugs used are operating through known, specific neurotransmitter mechanisms; a contention that very often must be revised in light of new pharmacological data.

Progress in more physiological assessments, such as looking at the spontaneous changes in neural activity and levels of endogenous neurochemicals concomitant to behavioral processes, has been delayed by the lack of adequate methods. In recent years, however, many powerful tools for analyzing neurobiological functions have been developed, and some of them have been applied succesfully to the analysis of physiological correlates of masculine sexual behavior. As a result, there is already a sizeable body of information about changes in several indices of CNS function, including some neurotransmitters and related substances, associated with different aspects of sexual behavior. This review summarizes the main findings, attempting to bring together a somewhat dispersed information. As with so many other aspects of the experimental analysis of male sexual behavior, most of the published reports are based on the rat. When available, data from other species are discussed as well. Likewise, experimental findings in females are presented occasionally for comparison with males or when they are the only existing data. Not surpringly, the experiments reported to date using these relatively new methodoologies have focused on the CNS areas which, according to the existing large body of evidence from lesion and stimulation studies, seem to have more prominent roles in the regulation of sexual behavior. They are briefly outlined in the following paragraphs. For a thorough discussion of this topic the reader is referred to a set of excellent, relatively recent, reviews (58,82,163).

The medial preoptic area has long been recognized as "the single most critical region for the mediation of male sexual behavior in mammals" (82), since its lesion leads invariably to the loss of mating activity in all the species studied. Yet, the motivational aspects of sexual behavior, as evidenced by the persistence of precopulatory appetitive responses, are preserved in animals bearing preoptic lesions (58). On the other hand, various components of the consummatory system, such as the erectile reflexes or the seminal emissions displayed in ex copula tests remain unimpaired following preoptic lesions (174). Thus, it is currently thought that the key role of the medial preoptic area in mating activity probably lies in the translation of sexual arousal into appropriate copulatory motor patterns (58, 163).

The appetitive components of sexual behavior can be altered by manipulations of the dopaminergic innervation of the ventral striatum, including the nucleus accumbens (58). The latter is regarded as a functional interface between the limbic and motor systems involved in the translation of affective and motivational states into behavioral acts, a process in which its dopaminergic innervation would have a "gating" role (133). The dorsal striatum, a major component of the motor system, and its prominent dopaminergic innervation have not been ascribed specific functions in the regulation of mating activity, but this behavior can be hampered by the severe impairments of motor function which often follow their lesions (e.g., 156). Other forebrain regions, notably the olfactory bulbs and some nuclei of the amygdala have also been attributed significant roles in the regulation of masculine sexual behavior at precopulatory stages, probably participating in the associative mechanisms by which environmental stimuli translate into appetitive sexual responses (58). Some brainstem areas, especially the tegmental region, seem to participate in the pacing of copulatory activity, whereas the basic reflexive elements for penile erection and ejaculation are contained in the lower levels spinal cord, with important modulatory influence descending from the brain. There are some other CNS structures, such as the hippocampus, the septum, or some hypothalamic nuclei that have been documented as able to influence masculine sexual behavior too, although less consistently than the preceding areas. They have been occasionally studied in some of the experiments discussed here.

The search for functional changes in these CNS areas during mating and related phenomena has been done with a variety of ex vivo and in vivo methodologies. The former are applied on samples of neural tissue taken when the animals are sacrificed shortly after the display of some aspects of the behavioral pattern being studied or following exposure to relevant stimuli. For in vivo studies, the experimental animals are implanted with probes designed to monitoring different aspects of brain function simultaneously with ongoing behaviors. The basic principles underlying these procedures are briefly commented on, including their relative advantages and limitations, together with the reported experimental findings related to male sexual activity.

EX VIVO STUDIES

This approach is based on the assumption that the changes found in tissue samples obtained postmortem reflect the neurochemical processes that were taking place in the brain at the time of sacrifice. To date, the aspects of neural activity that have been assessed in connection with sexual behavior by ex vivo analyses of CNS fragments include markers of energy metabolism such as 2-deoxyglucose uptake and Na,K-ATPase activity, the content and turnover of some neurotransmitters and modulators, immediate-early gene expression products, and gonadal hormone receptors and neurosteroid levels.

BRAIN METABOLIC ACTIVITY

2-Deoxyglucose Autoradiography

Radioactive glucose analogs that cannot be metabolized and accumulate in the cells, such as 14C-2-deoxyglucose (2DG), can be used for estimating the rate of local glucose consumption. Combined with autoradiographic techniques, they provide a semiquantitative index of metabolic activity in different brain areas (100). The 2DG method has been used for studying regional changes in energy metabolism associated to several aspects of brain function, including some behaviors.

The studies applying this methodology to the analysis of sexual behavior are, however, limited in number and scope. Thus, increased 2DG accumulation has been found in the lateral hypothalamus of male rats exposed to female odors (144), whereas no changes were observed in other brain regions including the medial preoptic area, the dorsomedial hypothalamus, the lateral septum, and the corticomedial amygdala. In another experiment, conditioned sexual arousal was assessed in male rats which were given a sham injection previously associated to the presence of an estrous female behind a wire mesh. Increased 2DG accumulation was found in three amygdaloid nuclei whereas there were no changes in the lateral hypothalamus, the medial preoptic area and the nucleus accumbens (47). Studies in females have shown increased 2DG uptake in areas such as the medial preoptic, the bed nucleus of the stria terminalis, the mesencephalic reticular formation, and the globus pallidus of rats undergoing vaginocervical