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Brain and Sexual Behavior

KNUT LARSSONa,c and SVEN AHLENIUSb

aDepartment of Psychology, University of, Göteborg, Box 500, SE-405 30, Göteborg, Sweden
bDepartment of Physiology and Pharmacology, Karolinska Institute, S-171 77 Stockholm, Sweden

cVoice: +46-31-7731641; fax: +46-31-7734628; knut.larsson@psy.gu.se

ABSTRACT

This chapter will give personal accounts of the neural basis of male rat sexual behavior from two somewhat different perspectives, one tilted towards neuroanatomy (K.L.), and one tilted towards monoaminergic pharmacology (S.A.). Both perspectives were strongly influenced by the Zeitgeist, the former imperceptibly merging into the latter as relations between the neural substrate for monoaminergic neurotransmission was elucidated. 1

THE NEUROANATOMICAL PERSPECTIVE

Introduction

In the late 1940s, when I began my graduate studies, psychology and physiology still had not met as scientific disciplines. Animal behavior was studied in the American laboratories of psychology but not in its relation with physiological processes. Hull 2 and Skinner, 3 the leading behaviorists at the time, both framed models of operant and instrumental conditioning. Hull conceptualized physiological processes as intervening variables without making any attempts to define and characterize them further. Skinner was equally certain that concepts like intervening variable were unjustified and even scientifically unsound, specifying stimulus-response relationships as all that was needed.

In Europe, the behavior of mammals was studied systematically by the ethological school with leaders like von Frisch, Lorentz, and Tinbergen as towering figures. The ethologists assumed inborn "instincts" as organizers of behavior. By instincts 4 was meant inherent, species-typical behavior patterns that were assumed to have developed under the pressure of evolution like the morphological and physiological features of the species.

The behaviorists and the ethologists differed in methods and outlook on science. The behaviorists formulated problems that allowed the use of animals to answer research questions in behavioristic terms and gave a methodology that would permit fine-grained analysis of the behavior. A main contribution of the ethologists was observation of animal behavior in the wild as part of the animal's normal life and their emphases on the evolutionary perspective. The behaviorists considered individual experience as the main organizer of behavior, whereas the ethologists focused on species variations determined by the genome. In one respect, however, the approach to behavior of the two schools was similar. Both thought that the behavioral analysis was a prerequisite to obtaining a complete explanation of the behavior. None was concerned with the role of the brain in the regulation of behavior, or, for that matter, of the importance of any measures relating molar and molecular event. None anticipated the explosive rise of physiological psychology, nor the development of behavioral neuroscience soon to come.

I had from my early school days been curious about animal behavior and its physiological bases, but when I entered the university in the midst of the 1940s, psychology did not even exist as a separate subject in the Swedish universities. I wanted to approach animal behavior in a way that allowed me to study behavioral and physiological variables in their interaction. I happened to hear that in Norway there was an anatomist, Alf Brodal, and a neurophysiologist, Birger Kaada, who both tried to relate anatomy, physiology, and behavior to each other. So I went to Oslo. At the Anatomical Institute in Oslo, where both these researchers worked, I was given the task of studying the female mouse estrous cycle. This study became a revelation for me. Sitting at night in the animal room and looking at the behavior of the mice, I felt I was looking down directly into nature itself. I observed each fourth

day, how the female mouse, within a matter of an hour, entered a state of receptivity when her rejection of the male was turned into acceptance. The behavioral cyclicity was a reflection of endocrine, morphological, and neuronal changes, controlled by the brain. Brodal, once a student of Judson Herrick, gave me the attractive book of his teacher, *The Brain of Rats and Man*, together with his own writings on the limbic brain. [5] Kaada, who had done his Ph.D. studies during the war with John Fulton at Yale university, gave me his work on electrical recordings from the brain. [6] These experiences made me decide to study reproductive behavior, which, in such a wonderful way, twins hormonal, neural, and behavioral influences.

Some years later, now with a doctoral degree in male rat sexual behavior completed, I met Lennart Heimer, who just had ended his medical studies and had even written an introductory textbook on neuroanatomy for medical students, the first Swedish book of this kind. Joined by our common interest in brain and behavior, we began to work together looking for brain correlates of sexual behavior. I will, to begin, outline the main lines of this work. Questions proposed during the course of these studies prepared for later studies that were oriented towards neurotransmitters possibly involved in sexual behavior. These problems will be dealt with in the second part of this report.

Central Neural Control of Male Rat Sexual Behavior

As a background for the experiments to be described below, Figure 1 depicts male rat sexual behavior. [7] When exposed to a receptive female, the experienced male approaches her and mounts her. After repeated mounts and intromissions, ejaculatory behavior is elicited. The ejaculation is followed by a refractory period when the male is sexually unresponsive. After 4-5 minutes, he resumes pursuance and mounting of the female. Mounts, intromissions, and ejaculations can be easily recognized, counted, and expressed in terms of frequency and latency of their first appearance. It is assumed that the intromissions cause a rising sexual excitation cumulating in ejaculation.

FIGURE 1. Schematic presentation of the male rat copulatory performance. [7]

When Lennart and I begun our studies in the beginning of the 1960s, little was known about the role of the brain in the regulation of sexual behavior. Removal of large parts of the cerebral cortex, independently of their localization, disrupted copulation in males of several species. [8] Later studies [9] showed, however, that lesions in the medial-frontal cortex abolished mating in some rats, whereas lesions in the more posterior regions, including the cingulate gyrus, had little or no effects on mating, suggesting different roles of frontal and posterior parts of the rat cortex. It was not until the end of the 1940s that stereotaxic surgery was introduced into the laboratory, allowing investigators to place discrete lesions within the depths of the brain. [10] It was reported that electrolytic lesions in the hypothalamus impaired male rat sexual behavior without causing any apparent hormonal deficits. [11,12] The subcortical lesions performed in these studies were, however, too large to admit localization of the behavioral impairment to any specific group of cells. Therefore, Lennart and I decided, as a first task, to locate the neural circuits essential for the sexual behavior. For this we needed a stereotaxic instrument. We built such an instrument, with the help of Victor Kuikka, the skillful technician of the anatomy department. [13]

Not knowing where to begin, in the anterior or the posterior end of the brain, we decided to start in the rostral end of the brain stem to continue forward. We made two interesting findings (Fig. 2). First, extensive lesions in the junction of the diencephalon and mesencephalon made them hypersexual. [14] The males ejaculated after only a few intromissions, within a very short time, and showed abnormally shortened PEIs. Within an hour, some males had ejaculated a dozen times compared to three or four times normally. Our second finding pertained to lesions in the area of the medial preoptic nucleus and the anterior hypothalamus (MPOA). Extensive lesions in this area abolished sexual behavior seemingly permanently; minor lesions in this area, independent of location, caused only a temporary impairment of the behavior. [15] Both these findings led us to suggest two neural mechanisms regulating male rat sexual behavior, one involving subcortical structures in the caudal diencephalon and anterior mesencephalon, exerting an inhibitory influence upon mating, and another mechanism located in the MPOA, mediating sexual arousal and controlling the motoric aspects of mating.

FIGURE 2. *Top*: Outline of individual lesions in the medial preoptic-anterior hypothalamic continuum that eliminated mating behavior. [15] *Bottom*: The figure demonstrates the reduction of the postejaculatory intervals and the accompanying increase in ejaculation frequency in one male rat subjected to lesions at the junction of the diencephalon and mesencephalon. The behavior was observed during three subsequent 60-min tests. Filled circles represent the median values of the postejaculatory intervals recorded during these tests. Vertical lines represent maximal and minimal values. Open circles represent the corresponding performances of a group of 31 intact males.

The medial preoptic-anterior hypothalamic continuum occupies a strategic position in the limbic system (Fig. 2). Its lateral zone is an interstitial nucleus of the medial forebrain bundle, a polysynaptic fiber system that provides a major reciprocal link between the medial basal telencephalon rostrally and the midbrain tegmentum caudally. It is located outside the main stream of the medial forebrain bundle, but it is known to receive numerous short fibers from the lateral zone, making its functional state likely to be influenced by impulses arriving in the hypothalamic region by way of the medial forebrain bundle. [16] Such impulses are supposed to originate from visceral and somatic sensory structures of the lower brain stem, from the hippocampus, cingulate cortex, septal area, and amygdaloid complex. Of equal relevance should be axons to the medial forebrain bundle arising from olfactory structures, such as the piriform cortex, the olfactory tubercle, and the olfactory lobes. [17]

FIGURE 3. Cumulative percentage of male rats showing ejaculation in 26 daily mating tests following surgical destruction of the main olfactory lobes or sham operation at 30 days of age. Peer-deprived rats were reared in single cages from 10 days of age until the end of testing. Group-reared rats lived together with two female litter mates.

Besides its more diffuse afferent connections from the lateral hypothalamic zones, the MPOA receives a component of the stria terminalis, a major fiber system originating in the amygdaloid complex. [18] The stria terminalis, in part at least, originates from the cortico-medial subdivision of the amygdala, a region known to receive numerous fibers directly from the accessory olfactory lobes. [19] The position of this intermediate area between what was then called the limbic and olfactory telencephalon on the one hand, the midbrain tegmentum on the other hand, and bordering the gonadotrophic mechanisms of the tuberal hypothalamus was compatible with our finding that this region is important for the regulation of mating. Considering the highly heterogeneous, multimodal afferent relationships, among which the olfactory modality appeared to be particularly strongly represented, we decided to focus on the role of the olfactory system and moved, thereafter, in the posterior direction, being interfered with by lesions at various levels of the limbic system. Failing any good anatomical guidance, Lennart started to study the basal forebrain using various silver-impregnation techniques. Soon he had developed a technique of his own, later to be published as the Fink-Heimer technique. [20]

Electrolytic lesions of the main olfactory bulb, or surgical section of the lateral olfactory tract, impaired, but did not prevent, the occurrence of sexual behavior. [21] Further work was undertaken involving destruction of the main olfactory bulb or sectioning of the lateral olfactory tract. Again, we found a striking variation of the behavioral effects obtained, suggesting a role for factors other than olfaction, as such (Fig. 3). We soon discovered that sexual experience was one of these disturbing factors: those males that were sexually naive when made anosmic rarely ever started to mate. The sexually experienced males, by contrast, showed relatively small effects of anosmia. [22-24]

FIGURE 4. Effects of median and dorsal raphe electrolytic lesions on male rat copulatory behavior. The FIGURE shows medians ± semi-interquartile range. Sham-lesioned controls from two groups were pooled and are shown by the shaded area. Statistical comparisons with sham-lesioned controls were performed by means of the Mann-Whitney *U*-test, as shown in the Figure. ns, $p > 0.05$; $*p > 0.05$. For further details see Ahlenius and Larsson. [6]

The observation of the importance of experience for sexual behavior came as a complete surprise to

us. From the considerable literature on sex and olfaction existing at that time, we were made to believe that odoiferous signals were mainly coupled with preprogrammed behaviors. Our observation, however, pointed at a powerful role of olfactory memory. More recent work has confirmed these observations, and, in addition, indicated the importance of the vomeronasal organ and the accessory olfactory lobe in such a mechanism. [25] It appears that the sense of olfaction is particularly well suited for storing emotionally important memories. [26]

After these studies were concluded, Lennart went to Walle Nauta at MIT to continue his neuroanatomical work, which he had begun in Sweden. This research was going to result in this conceptual remodeling of the basal forebrain that we are discussing here. As I have tried to show you, this research program was guided by a need to find ways to explore the role of the brain in behavior, and reproductive funtions, in particular. The work subsequently performed by Lennart and his associates has shown the role of a collection of structures, including the nucleus accumbens, olfactory tubercle, septum, diagonal band nuclei, and bed nucleus of stria terminalis as well as the extensive territory beneath the temporal limb of the anterior commissure, which long was referred to as the substantia innominata. [27] Of special importance to reproductive funtions is the ventral striatopallidal system, the extended amygdala, and the areas of transition between these two systems. [18] The concept of a critical role of the MPOA in mammalian sexual behavior has been confirmed in all mammals studied. [27] The MPOA, the bed nucleus of stria terminals, and the medial nucleus of the amygdala are reciprocally connected anatomically, and the medial nucleus of the amygdala receives direct projections from the main and accessory olfactory lobes. [29,30] An additional input from the main olfactory lobe is received by afferents from the cortical nucleus of the amygdala. [30] Pathways linking the cortiocomedial amygdala with the bed nucleus of stria terminalis may convey impulses generated by chemosensory receptors of the olfactory systems promoting sexual arousal. This applies in various degrees, to all mammals, including humans. In view of the major importance of gonadal hormones for sexual behavior, it should be noted that all of these areas are densely packed with gonadal hormone receptors. [28] These receptors are closely associated with enzymatic systems that process the prehormones to active agents. [31-33]

THE MONOAMINERGIC PERSPECTIVE

Introduction

Returning to the early 1960s, Arvid Carlsson, Åke Hillarp, and their students in the pharmacology department close to our laboratory in Göteborg were studying another aspect of brain physiology, namely neurotransmitters. Dopamine (DA) and 5-hydroxytryptamine (5-HT) had just been discovered as having functions of their own as neurotransmitters. The neurons producing these substances could be visualized by the histofluorescent methods, then newly reported. We looked upon the pictures of the rat brain offered to us, showing skies of neurons, in deep green, transferring catecholamines, and, in bright yellow, eurons using 5-hydroxytryptamine. The neurons were longer than had ever been seen, stretching out between the brain stem and the forebrain. [34-39] Naturaturally, we were eager to know more about the function of these neuronal systems.

Dopamine

Dopamine (DA) is involved in all aspects of sexual behavior, including sexual arousal, copulation, and penile reflexes. [40] Exposing the male rat to a receptive female, we found a selective increase in the synthesis of DA in the nucleus accumbens. [41] Further studies indicated that this increase is characteristic of sexually naive rats and does not occur in experienced ones, suggesting a role of DA in the novelty aspect of sexual stimulation rather than sexual activity, as such. [42]

Dopaminergic projections from the substantia nigra and ventral tegmentum pass to the ventral striatum and nucleus accumbens, respectively. [43] DA activity is reduced after localized lesions are produced by treatments with a neurotoxin, 6-hydroxydopamine. Further, systemic treatment with both DA D_2 and mixed DA $D_{1/2}$ receptor antagonists in these areas reduces the level of sexual arousal as assessed by prolonged mount and intromission latencies and PEIs, without accompanying alterations of the copulatory activity. [44-50]

The administration of a variety of DA agonists enhances the copulatory activity, and this effect is reversed by treatment with DA D_2 receptor antagonists, as evidenced by a reduction of the ejaculation

latency. 51-54 The MPOA is the only site of action identified for the stimulatory effect of DA in copulatory activity. Such dopamine receptor agonists as apomorphine, quinpirole, and lisuride stimulate copulation, penile erection, and seminal emission; their effects are reversed by DA receptor antagonists. The stimulatory effect on penile erection requires the presence of testosterone and appears to be mediated postsynaptically. 55 The stimulation of penile erection originates in the paraventricular nucleus, because injection of DA agents in this nucleus induces penile erection combined with **yawning**, 56,57 an effect probably mediated by a release of oxytocin. 58

Noradrenaline

The noradrenergic system originates in the locus caeruleus and innervates the entire forebrain. It stimulates sexual activity probably in an indirect way but has an inhibitory role on penile erection. 59-61 Lesions of the locus caeruleus, inhibition of noradrenaline (NA) synthesis, and inhibition of NA release by 2-andrenoceptor agonists are all agents causing a prolongation of ML, IL, and PEI. 62 Yohimbine, an 2-adrenoceptor antagonist, has repeatedly been reported to be effective in stimulating sexual activity, presumably because the NA cell bodies in the nucleus caeruleus are under tonic 2-adrenoceptor influence. 59,60,63

5-Hydroxytryptamine

Central brain serotonergic systems were long considered to inhibit the neural mechanisms regulating male and female sexual behavior. This contention was based on (l) the observation that a decrease in brain serotonin facilitates ejaculation in rats, as evidenced by a decrease in the number of intromissions to ejaculation and a shortening of the ejaculation latency and (2) the observation that an increase in availability of synaptic 5-HT inhibited the behavior, as evidenced by an increased number of intromissions and a prolonged ejaculation latency (see ref. 7). A behavioral facilitation was produced by the inhibition of tryptophan hydroxylase by treatment with p-chlorophenylalanine, 64,65 selective destruction of brain serotonergic neurons by 5,7-dihydroxytryptamine, 66 or electrolytic lesions of serotonergic projections from the raphe nucleas to the MPOA. 67

The major sources of serotonergic innervation of the forebrain are the dorsal (DR) and median (MR) raphe nuclei. 68 A study was undertaken of the effects on masculine sexual behavior of lesions aimed specifically either at the median or the dorsal raphe nuclei. 7 In parallel experiments we checked the specificity of the lesions by examining the 5-HT decrease in target areas. The MR lesions produced a relatively greater decrease in septal than in neostriatal 5-HT content: the DR lesions produced the opposite pattern. The MR lesions caused a marked facilitation of sexual behavior, as evidenced by a decrease in the number of intromissions to ejaculation and a shortening of the ejaculation latency and of the postejaculatory intervals. No changes in the mating behavior were observed after DR lesions (Fig. 4). These results receive further support from pharmacological studies. 69

In our efforts to characterize the role of the serotonergic transmitter systems in the regulation of sexual behavior, we were given access to a new substance, 8-OH-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). This substance was developed at the Department of Pharmacology, University of Göteborg, and at the Department of Organic Pharmaceutical Chemistry, University of Uppsala, and was characterized as a 5-HT receptor agonist. 70 We expected that this compound would inhibit the behavior. Instead we found that 8-OH-DPAT produced a drastic facilitation of the ejaculation reflex. The number of intromissions was lowered and the time to ejaculation shortened. Sometimes the male ejaculated after one single intromission, resulting in an *ejaculatio precox*-like effect 7 (Fig. 5).

FIGURE 5. Facilitation of male rat ejaculatory behavior by the administration of the 5-HT1A receptor agonist, 8-OH-DPAT. The Figure shows medians ± semi-interquartile range based on repeated observations of the same animals in a changeover design. Statistical analysis was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks *t*-test, for comparisons with saline-treated controls, as shown in the Figure. ns, $p > 0.05$; * $p < 0.05$; ** $p < 0.01$. For further details see Ahlenius *et al.* 86

This highly specialized 5-HT receptor agonist we had received in our hands was soon shown to have high affinity to a subtype of receptor named the 5-HT1A receptor. 71 It had been known earlier that certain ß-blocking agents, like propranolol and pindolol, could antagonize behaviors involving the 5-

HT receptor. These compounds, having selective affinities to 5-HT1A receptors, antagonized the facilitation of the ejaculation reflex induced by 8-OH-DPAT. Recently another, more selective 5-HT1A receptor blocker, WAY-100635, was found to have the same effect. These and other observations suggest that 8-OH-DPAT exerts its dramatic effect upon male rat sexual behavior by stimulating 5-HT1A receptors in the brain. Several other compounds with high affinity for the 5-HT1A receptor, including buspirone, flesinoxan, and FG 5893, have later been shown to share the effects of 8-OH-DPAT on ejaculation behavior. [72,73]

In order to examine a possible site of action for these effects, we locally applied 8-OH-DPAT to two sites in the ventral forebrain and also onto cell bodies of origin in the DR and MR. Infusion of 8-OH-DPAT in the MR accelerated the rate of copulation, possibly by stimulating 5-HT1A somatodendritic autoreceptors, thereby causing an inhibition of neuronal 5-HT activity. [69,74] No facilitation was produced by infusing 8-OH-DPAT into the DR. The median raphe injections decreased 5-HT synthesis in the nucleus accumbens, the ventromedial striatum, and the amygdala, as well as in the hippocampus and the septum. Also the DR injections of 8-OH-DPAT produced a decreased 5-HT synthesis in the forebrain, but the effects were most pronounced in the dorsolateral striatum and the globus pallidus. Summarizing these observations, we conclude that the MR belongs to a midbrain neural system, inhibitory to sexual behavior.

Also experiments with 5-HT clearly demonstrated region-selective effects. Local application of 5-HT into the nucleus accumbens inhibited sexual behavior, whereas local application into striatal areas ventral or dorsal to this site produced no effects. [69] The local application of 5-HT onto serotonergic somatodendritic autoreceptors in the DR and the MR facilitated the behavior. [75]

If activation of 5-HT1A receptors mediate a facilitatory influence on sexual behavior, the inhibitory influence obtained after treatment with 5-HTP must be a consequence of stimulation of other receptors. One of them may be the 5-HT1B receptor. Several pharmacological agents selectively stimulate this receptor, resulting in an increase in the number of intromissions and prolongation of the response latencies. [76] Another class of 5-HT receptors is the 5-HT2 receptor. Treatment with DOI, a selective 5-HT2A/C receptor agonist, inhibits male sexual behavior, an effect that is blocked by selective 5-HT2/5-HT1C antagonists, like ritanserin and ketanserin. [77] Unlike the effects produced by the various 5-HT1-selective receptors, this last effect does not seem to be an effect specific to the ejaculation behavior and may not even be specifically associated with sexual behavior. This raises the problem of possible differences between 5-HT2A and 5-HT2C receptors. New and selective pharmacological tools will probable soon be available to clarify the role of different 5-HT2 receptors in male sexual behavior.

Treatment with 5-HTP presumably results in an increased release of 5-HT at all serotonergic synapses. In a series of recent studies, we asked whether treatment with selective serotonin antagonists even influences the inhibitory effects produced by 5-HTP. By antagonizing the effect of 5-HTP on the 5-HT1A, receptor we would receive a potentiation of the inhibitory influence produced by 5-HTP. Male rats were injected with 5-HTP combined with benserazide, and thereafter treated with either WAY-100635 (5-HT1A receptor antagonist), isamoltane (5-HT1B receptor antagonist), or ritanserine (5-HT2A/C receptor antagonist). We found that WAY-100635 potentiated the effects of 5-HTP, whereas isamoltane blocked these effects. The ejaculation pattern remained unaffected by ritanserin. These results support the hypothesis that 5-HTP stimulates as well 5-HT1A as 5-HT1B receptors, the net effect of 5-HTP representing a balance between activation of these two receptor types. [78]

It is worth noting that the drug effects on male rat ejaculatory behavior reported here are very different from their effects on penile erections. Thus, 8-OH-DPAT, which facilitates ejaculatory behavior, inhibits penile erections. [79,80] Furthermore, the nonselective 5-HT1B receptor agonist, 1-(3'-chlorophenyl)-piperazine (mCPP), induces penile erections (ref. 81, cf. ref. 82), whereas the 5-HT1B receptor agonist, anpirtoline, inhibits ejaculatory behavior. [83] Finally, stimulation of 5-HT2C receptors (formerly the 5-HT1C receptor) induces penile erections. [82-85]

CONCLUDING REMARKS

Let us trace our journey together. In the beginning, the problem was to find an approach to behavior that would reasonably well lend itself to an analysis of underlying biological mechanisms. Reproductive behavior, turned out to be eminently suited for this purpose: essential for the survival of the species, shaped along with other morphological and physiological features of the species, yet not of critical importance for survival of the individual. Furthermore, it is a behavior dependent upon the senses and hormonal regulation, intricately linked to brain functions. Few neuroanatomists or psychologists in the late 1950s thought about behavior in these terms. After the first fumbling attempts to find the brain structures involved in the control of male rat sexual behavior, we discovered how little was known of the neural organization of the brain, not least of which were those circuits that controlled reproduction. From a different perspective, this surely was a challenge for Lennart Heimer to devote himself to in-depth studies on the neural organization of the basal forebrain. The new conceptualization he has brought to this brain territory has been a great gift to all investigators in the fields of psychoactive and emotional behavior, including behavioral functions related to reproduction. The parallel discoveries of monoaminergic neurons connecting mesencephalic and lower brain stem structures with all other parts of the nervous system was revolutionary. Coupling these insights with the wiring and neuroanatomical delineation of structures in the basal forebrain not only shed new light on relations between brain and behavior, but also opened the possibility of exploring brain functions with pharmacological probes. Anatomy and pharmacology became two sides of the same coin.

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