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CNS arousal mechanisms bearing on sex and other biologically regulated behaviors

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Abstract

It now seems possible to move beyond analyzing only the mechanisms for specific sexual behaviors to the analysis of 'generalized arousal' that underlies all motivated behaviors. Our science has advanced sufficiently to attack mechanisms linking specific motivations to these general arousal mechanisms that intrinsically activate all biologically-regulated behaviors including ingestive behaviors. Learning from the well-developed reproductive behavior paradigm, we know that sex hormone effects on hypothalamic neurons have been studied to a point where receptor mechanisms are relatively well understood, a neural circuit for a sex steroid-dependent behavior has been worked out, and several functional genomic regulations have been discovered. Here we focus for the first time on three chemical systems that signal 'generalized arousal' and which impact hormone-dependent hypothalamic neurons of importance to sexual arousal: histamine, norepinephrine and enkephalin. Progress in linking generalized arousal to specific motivational mechanisms is reviewed.

Keywords: Estrogen; Hypothalamus; Sex; Estrogen receptor; Arousal; Histamine; Norepinephrine; Opioid; Enkephalin; Lordosis; Courtship

1. Introduction

This paper reviews the first steps in linking mechanisms for well-studied biologically-regulated behaviors to underlying states of generalized arousal. In the past we chose an extremely simple behavior in order to answer the question "Is it possible to explain detailed cellular and genetic mechanisms for *any* mammalian behavior?" Now, progress in our field allows us to ask the question "Can we begin to approach mechanisms for CNS arousal functions that underlie *all* motivated behaviors?" Here, we begin by briefly reviewing some aspects of the work on sex behavior and then recount some of the progress linking sex behavior to CNS arousal.

The simplest behavior obtainable in its natural form in the laboratory and essential for reproduction is lordosis behavior. The entire neural circuit for the production of lordosis behavior has been elucidated and its modules illustrated [1,2]. In the absence of fear- or anxiety-provoking conditions, females under the influence of estrogens plus progestins (E+P) will demonstrate courtship and then mating behaviors. During the normal female cycle, these behavioral components of reproduction are synchronized with ovulation. Thus, with the mediation of estrogens plus progestins, the neural, behavioral and endocrine preparations for reproduction are harmonized.

2. Direct effects of estrogens, from gene induction to neural circuit to behavioral change

Typically, we compare two extremely similar transcription factors, estrogen receptors (ERs) alpha and beta. Likely gene duplication products, both have high affinity for estradiol and for genomic estrogen response elements (EREs) in vertebrate gene promoters [3–6]. Yet, they have distinctly different neuroanatomical patterns of expression [7] and different functional consequences.

Mong and Pfaff [8] have tried systematically to conceive of the biologically adaptive functions of estrogen-induced genes. This resulted in a theoretical approach called the 'GAPPS' model: *G*, for hormone-stimulated neuronal growth; *A*, for amplification by estrogen-induced progesterone receptors; *P*, preparation for reproduction by early, indirect facilitating behaviors; *P*, for permissive actions of

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estrogen-sensitive hypothalamic neurons on the rest of the lordosis behavior circuit; and *S*, for the synchronization of mating behavior with ovulation.

Of particular relevance to the linkage of lordosis behavior with CNS arousal are the estrogenic effects on neurotransmitter receptors in ventromedial hypothalamic (VMH) neurons that directly trigger the rest of the lordosis circuit to operate.

Noradrenergic alpha-1B receptors are induced [9] *in vivo* in female rats by estrogen treatment in VMH cells which govern the rest of the lordosis behavior circuit [10,11]. Noradrenergic ascending afferents synapse onto VMH neurons; they come in from the ventral noradrenergic bundle, which originates in arousal-related neuronal groups A1 and A2, and signals heightened arousal upon stimulation from the male. In biophysical studies, directly applied noradrenaline (NA) increases the electrical activity of VMH neurons [10]. Beginning with G_q or G_{11} proteins activating phospholipase C (PLC), NA action will produce both diacylglycerol (DAG), a protein kinase C (PKC) activator, and inositol 1,4,5-trisphosphate (IP_3), which mobilizes intracellular calcium. This signal transduction route is predicted to lead to L-type Ca^{2+} channel opening as in the heart, but this needs to be established. The induction of alpha-1B receptors by estrogen treatment is consistent with the greater electrophysiological effectiveness of NA following estrogen, but the detailed step-by-step transduction route to the channel now provides a timely subject for analysis. Since these VMH neurons are at the top of the lordosis behavior circuit, the NA effect fosters reproductive behavior.

Muscarinic receptors responding to the neurotransmitter acetylcholine are also expressed in VMH neurons [12] and are important for lordosis behavior [13]. Estrogen treatment increases their activities as determined electrophysiologically. Inputs to VMH neurons come from, among other places, the lateral dorsal nucleus of the tegmentum. Neurons are parts of the ascending arousal pathways, and would signal stimulation from the male upon mounting the female. We note that the apparent redundancy between ascending noradrenergic and muscarinic cholinergic afferents to the hypothalamus helps to guarantee that the system will not fail, and so exemplifies a design characteristic prominent in brainstem arousal system neurobiology. In any case, inducing muscarinic receptors increases the VMH cellular electrophysiological response to acetylcholine. Whether the estrogen effect employs a membrane receptor, a signal transduction mechanism or a classical genomic facilitation is not yet known. However, it is known that the enhanced VMH neuronal output primes lower pathways in the circuit for lordosis behavior.

3. Indirect effects of estrogens, from gene induction to downstream genes to behavioral change

Some hormone effects occur early, long before the onset of reproductive behaviors, and set the stage for later developments.

3.1. Neuronal growth

Growth promotion by estrogens in VMH neurons, in female rats, follows from the stimulation of synthesis of ribosomal RNA, which precedes the elaboration of dendrites and synapses on VMH neurons observed after hormonal treatment. The earliest estrogen effect is the increase of transcription of ribosomal RNA [14], followed rapidly by morphological effects, including those in the nucleolus itself [15] and a striking elaboration of rough endoplasmic reticulum in the cytoplasm [16]. Woolley and Cohen [17] have shown, probably consequent to the phenomena above, a stimulatory effect of estrogen treatment on dendritic growth. In the female rat hypothalamus, Frankfurt [18] and Flanagan-Cato [19,20] have reported that estrogens foster dendritic growth and, in agreement with this, other authors have reported an increased number of synapses [21]. Therefore, in VMH cells which control lordosis behavior circuitry, estrogens apparently provide the structural basis for increased synaptic activity and, therefore, greater sex-behavior-facilitating output. While the greater signaling capacity of these VMH cells thus proposed is consistent with the actual electrophysiological activity of such cells following estrogen treatment, the causal relation of structure to function still needs direct proof.

3.2. Amplification by progesterone

Administration of progesterone 24 or 48 h after estrogen priming greatly amplifies the effect of E on mating behavior. This effect requires the nuclear progesterone receptor (PR), as it disappears after antisense DNA against PR mRNA has been administered onto VMH neurons [22–24]. It also disappears in PR knockout mice [25]. Since PR itself is a transcription factor, effective when bound by P, its induction by estrogen might imply that certain downstream genes would, consequently, be upregulated. With molecular probes directed to specific genes, studied primarily in female rats, several genes have been revealed as upregulated by progesterone: these include neuropeptide Y receptor [26], galanin [27,28], oxytocin [29], gonadotropin-releasing hormone (GnRH) [30,31], mu opioid receptors [32], pro-opiomelanocortin [33], glutamic acid decarboxylase [34], a glutamate receptor [35] and tyrosine hydroxylase [36,37]. The manners in which these particular downstream genes contribute to reproductive behaviors will be exciting to explore.

3.3. GnRH

The physiological importance of estrogenic elevation of gonadotropin-releasing hormone (GnRH, LHRH) mRNA levels under positive feedback conditions – as well as elevation of the receptor mRNA for GnRH – would be to synchronise reproductive behavior with the ovulatory surge of luteinizing hormone (LH). The same GnRH decapeptide that stimulates the ovulatory release of gonadotropins also facilitates mating behavior [38,39]. In many small animals, synchrony of sex behavior with ovulation would be biologically adaptive because