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Role of acetylcholine in control of sexual behavior of male and female mammals

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ABSTRACT

The results of studies using systemic or central applications of cholinergic drugs suggest that acetylcholine makes important contributions to the neurochemical control of male- and female-typical reproductive behaviors. In males, cholinergic control seems largely specific to some elements or aspects of copulatory behavior that can vary significantly across species. Synapses in or near the medial preoptic area represent part of this mechanism, but the entire system appears to extend more widely, perhaps especially to one or more structures flanking some part of the lateral ventricle. In females, the lordosis response that essentially defines sexual receptivity is clearly responsive to cholinergic drugs. The same seems likely to be true of other elements of female sexual behavior, but additional studies will be needed to confirm this. Changes in cholinergic activity may help to mediate estrogenic effects on female sexual behavior. However, estrogen exposure can increase or decrease cholinergic effects, suggesting a relationship that is complex and requires further analysis. Also presently unclear is the localization of the cholinergic effects on female sexual responses. Though periventricular sites again have been implicated, their identity is presently unknown. This review discusses these and other aspects of the central cholinergic systems affecting male and female sexual behaviors.

1. Introduction

Acetylcholine (ACh) was the first neurotransmitter to be described, setting the standards for the analysis of other possible transmitters (Van der Zee and Keijser, 2011). Crucial roles in behavior are assured if only by the prominence of cholinergic synapses in somatic and autonomic efferent pathways. But such synapses abound in the brain as well, suggesting that central cholinergic mechanisms also impact behavior. Though some such effects have been widely recognized (e.g., Klinkenberg and Blokland, 2010), others have attracted less attention. These include effects on the reproductive behaviors typical of male and female mammals. Yet studies in the past 50 years suggest that these are highly responsive to fluctuations in central cholinergic activity. This review aims to summarize our knowledge of the role played by central ACh in mammalian reproductive behavior, focusing on studies that implicate a specific system (nicotinic or muscarinic) and extending earlier reviews by Bitran and Hull (1987) and Dohanich (1995).

2. Brain control of reproductive behavior

Reproduction is complex behaviorally and neurally (e.g., Pfaff, 1980). Studies have sought to manage these complexities by focusing on the most obvious behaviors and most influential brain areas. With regard to the first, studies of male sexual behavior have emphasized the mounts, intromissions and ejaculations that stand out in copulating males. Similarly, studies of sexual behavior in females have focused on the lordosis responses that define sexual receptivity, the responsiveness of females to potential sexual partners.

Brain areas implicated in the control of male sexual behavior include the amygdala, bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA) and many others (review in Hull, 2010). Among all of these, the MPOA has been a focus of attention. It is thought to integrate hormonal and sensory inputs, helping to process both precopulatory stimuli and the feedback that emerges in the course of copulation. Its outputs are thought to influence sensory processing, sexual motivation, and the reflexive and other components of copulatory behavior.

Areas implicated in the control of lordosis and other female sexual responses include the lateral septum (LS), MPOA, periaqueductal gray (PAG), ventromedial hypothalamus (VMH) and others (review in Floody and DeBold, 2004). Attention again has been focused, in this case on the MPOA and VMH. These are thought to generate competing lordosis-inhibiting and -facilitating signals that are integrated in the

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PAG. But the emphasis on these structures again reflects roles thought to extend broadly, across different forms of sexual behavior and their many hormonal and other determinants.

3. Central cholinergic systems

Though cholinergic systems can be analyzed in many ways (Van der Zee and Keijser, 2011), the most useful description seems to be that provided by the distributions of ACh receptors. Because many receptors exist, their analysis has the potential to describe relations to behavior that are more specific than those suggested by other forms of evidence.

3.1. Nicotinic systems

Nicotinic receptors (nAChRs) are ionotropic, generally excitatory, and activated by nicotine (Changeux et al., 1998; Nashmi and Lester, 2006; Tribollet et al., 2004). Each contains five subunits drawn from five types, some of which themselves exist in multiple forms. This permits the assembly of many receptors differing in structure and possibly function. One major distinction is between muscle-, ganglion- and neural-type nAChRs. The last one includes high- and low-affinity subtypes that differ in their binding of agonists and α-bungarotoxin (this and all other drugs discussed here are described in Table 1). On the basis of their physiological properties, it has been suggested that low-affinity receptors are well-suited to modulatory effects whereas high-affinity receptors control more specific responses, especially in the areas of perception, memory and cognition (Tribollet et al., 2004).

High- and low-affinity nAChRs in the brain seem distributed in complementary fashions, with most areas containing moderate or high densities of just one or the other (Tribollet et al., 2004). The predominance of low-affinity receptors in structures including the amygdala, hypothalamus and LS (Nashmi and Lester, 2006; Pimlott et al., 2004; Tribollet et al., 2004) suggests that any effects of nAChRs on mating behavior are likely to revolve around this subtype.

3.2. Muscarinic systems

Muscarinic receptors are metabotropic and capable of excitatory or inhibitory effects (Levey et al., 1991; Vilaró et al., 1992). Five subtypes (M1–M5) have been distinguished by pharmacological and structural studies (Ehlert and Tran, 1990; Levey et al., 1991; Vilaró et al., 1992). Of these, M1 and M2 receptors were the first to be described and seem the best represented centrally. M1 receptors are reported to predominate in telencephalic areas including the amygdala, cortex and hippocampus whereas concentrations of M2 receptors have been described in diencephalic or brainstem areas including the hypothalamus (Ehlert and Tran, 1990; Gattu et al., 1997; Levey et al., 1991; Vilaró et al., 1992, 1994). M2 receptors also seem the most likely to function as autoreceptors, though this role seems open to all subtypes in one or another brain area (Levey et al., 1991; Murakami et al., 1996; Vilaró et al., 1992, 1994; Zhang et al., 2002). Together, these data suggest that M1 and M2 mAChRs are the most likely to impact mating behavior: They are the most common generally and seem to predominate in structures of special relevance to sexual responses, including the amygdala (M1) and hypothalamus (M2).

4. Cholinergic effects on male behavior

Studies of ACh's role in reproductive behavior have focused on responses to systemic or central applications of cholinergic drugs. Properly done, systemic studies can relate a behavioral element to a central change of a specific cholinergic type or subtype. But the more precise localization of an effect requires the observation of responses to appropriate central treatments.

4.1. Studies of possible nicotinic effects

Few studies have even attempted to relate mating behavior to changes in central nicotinic activity. However, several suggest that systemic treatment with low-moderate doses of nicotine alters male sexual responses to females, especially so as to reduce intromission frequency (Bignami, 1966; Retana-Marquez et al., 1993; Soulairac and Soulairac, 1975). In a quite different context, nicotinic effects on spontaneous erection have been observed in isolated male rats treated with cocaine after a period of paradoxical sleep deprivation (Andersen et al., 2004). Effects were observed, as expected on the basis of the link between ACh and paradoxical sleep (Andersen et al., 2004). In particular, erection frequency was decreased by either nicotine or mecamylamine, a blocker of nAChRs. This suggests that erection may require specific optimal levels of nicotinic activity, causing departures in either direction to cause behavioral declines.

The one relevant study using central treatments seems to be one by Hull et al. (1988a) in which male rats received carbachol or oxotremorine (OXO) injections into the MPOA or lateral ventricle. Whereas carbachol stimulates n- and mAChRs, OXO is a favorite muscarinic agonist. Therefore, responses that appeared only to carbachol seem likely to reflect central nicotinic effects. In this regard, Hull et al. found that only MPOA carbachol treatments increased mount and intromission latencies, suggesting nicotinic involvement in the processes that initiate these acts, and thus male copulatory behavior as a whole.

Together, these studies suggest that nicotinic mechanisms contribute to the control of male sexual behavior but fail to establish the extent or importance of these effects. In future work on this issue, any effects mediated by low-affinity nAChRs may be of special interest because of the predominance of these receptors in the brain areas most strongly linked to male sexual behavior. Though measures of intromission latency and frequency clearly merit attention, future studies also should recognize the possibility of effects on genital reflexes such as erection.

Table 1
Cholinergic drugs mentioned in the text.

Drug	Abbreviation, if any	System affected	Effect's direction	Effect's mechanism
α-Bungarotoxin		Nicotinic	Antagonist	Direct antagonist[a]
Atropine		Muscarinic	Antagonist	Direct antagonist
Bethanechol		Muscarinic	Agonist	Direct agonist
Carbachol		Both	Agonist	Direct agonist
Hemicholinium		Both	Antagonist	Synthesis inhibitor
Mecamylamine		Nicotinic	Antagonist	Direct antagonist
Methylatropine		Muscarinic	Antagonist	Direct antagonist[b]
Nicotine		Nicotinic	Agonist	Direct agonist
Oxotremorine	OXO	Muscarinic	Agonist	Direct agonist
Physostigmine		Both	Agonist	Acetylcholinesterase inhibitor
Scopolamine	SCO	Muscarinic	Antagonist	Direct antagonist

[a] α-Bungarotoxin preferentially blocks "low-affinity" neural-type nicotinic receptors.
[b] Methylatropine differs from the other drugs listed in its inability to cross the blood–brain barrier.